PRIMARY CARCINOMA OF THE LIVER

TO THE MEMORY OF

MY PARENTS

PRIMARY CARCINOMA OF THE LIVER

A STUDY IN INCIDENCE, CLINICAL MANIFESTATIONS, PATHOLOGY AND ÆTIOLOGY

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Produced by means of a grant from the South African Council for Scientific and Industrial Research



LONDON

H. K LEWIS & Co. Ltd.

1951

First printed . . . 1951

". . . . But if, after inflammation, the liver does not suppurate, the pain does not go off, its swelling changing to a hard state, settles down to scirrhus; in which case, indeed, the pain is not continued, and when present is dull; and the heat is slight; there is loss of appetite; delight in bitter tastes, and dislike of sweet, they have rigors; are somewhat pale, green, swollen about the loins and feet; forehead wrinkled; belly dried up, or the discharges frequent, the cap of these symptoms is dropsy."

ARETÆUS (*circa* A.D. 100–200)
Of Chronic Diseases, Book 1,
On Affections of the Liver: "Scirrhus Hepatis."

PRINTED IN GREAT BRITAIN FOR
H. K. LEWIS AND CO. LTD., BY
HAZELL, WATSON AND VINEY LTD., AYLESBURY AND LONDON

PREFACE

This monograph is an attempt to fill a gap in the literature of cancer, inasmuch as no comprehensive study of primary liver cancer is as yet available. In European literature the disease is still of academic interest only. Even the most authoritative text-books on medicine or pathology to-day devote only a few lines to the condition. Information on primary liver cancer must therefore be sought in current journals, many of which welcome the publication even of single cases.

Although numerous reports of primary liver cancer are available, rarity of the condition in Europe and America has prevented any single observer from following personally the clinical progress and pathology of an appreciable number of cases.

It has been my privilege, through its lamentable frequency in the male Bantu on the Witwatersrand, to gather together the clinical and pathological material of no fewer than 75 cases, of which 34 were under my own care. In addition, I have been able to analyse more than 700 cases recorded in the Bantu in different hospitals on the Witwatersrand gold mines and at the Johannesburg Non-European Hospital.

These studies have not been confined to the Bantu Available records from all parts of the world concerning primary liver cancer have been reviewed in the light of my own experience.

This book is the outcome of many years' interest in the subject, and is based on my M D. thesis and series of articles which appeared in the *South African Journal of Medical Sciences*. It is divided into four sections: the first is devoted to geographical and racial distribution, the second to clinical manifestations, the third to pathology, the fourth to the problem of ætiology. Brief reference is also made to the incidence of the disease in the lower animals I am hopeful that my work will prove of value to my colleagues and to those generally interested in the baffling problem of cancer.

As with other forms of malignant disease, the cause of primary liver cancer remains unsolved. For a considerable time, however, there has been a growing interest in many aspects of the problem and a formidable literature has accumulated. Perhaps the most impressive advances recorded thus far have been made in the laboratory, where it is becoming increasingly apparent that environmental factors play a vital role in the ætiology Indeed, few fields of cancer research have yielded more striking results than in the experimental production of primary liver tumours in animals.

The problem of therapy, however, has not yet received adequate attention. There is a singular lack of references concerning radium, deep X-ray therapy, radioactive substances, and other forms of treatment Surgery has proved of little value. It is sad to think that once the diagnosis has been established the patient's fate is sealed; nothing can be offered except palliative treatment As far as I am aware no attempts have been planned to elaborate curative methods, even in localities where the incidence of primary liver cancer is relatively common

In South Africa there is an influential body of opinion which to-day is strongly opposed to the idea of carrying out fundamental research in this country into the

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FOREWORD

The material obtained by Dr. Berman in his investigation of primary cancer of the liver in the Bantu, and the data which he has collected from a very scattered literature, seem to me to constitute one of the most valuable studies of cancer as it occurs in man which has appeared in recent years. The suggestions which his work, and that of some others in South Africa, offer of possible nutritional factors in the development and control of cancer have inspired a large amount of experimental work by myself and my colleagues. If the incidence of primary cancer of the liver were as great upon any large white population as it is upon the Bantu of South Africa, this disease would be held to constitute a major problem of cancer research.

The question, whether the prevalence of primary cancer of the liver in parts of Africa and Asia depends upon genetic or environmental factors, or upon both, is a fascinating problem which requires the collaboration of workers in many countries. Dr Berman has not only put forward the present state of the evidence very clearly: his monograph offers suggestions for research which are both practicable and of urgent importance. Thus the bibliography shows that we have at most half a dozen papers to inform us, in the matter in question, about the 400 million inhabitants of India, who present very diverse racial, economic and dietetic conditions The Negroes of America, who have lived for generations in a new environment, should obviously be compared with those of West Africa, yet we have no satisfactory data even from the United States, and none at all from South America. Dr. Berman has stated for us a question, the solution of which may throw light upon the whole problem of cancer.

E. L. Kennaway.

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INTRODUCTION

It is with pride as well as pleasure that I write this short introductory note to the wor of a South African who graduated in medicine at a South African university and is a officer in a South African whole-time medical service called into being at the behest o the State. Indeed, it is in his capacity as mine medical officer that Dr. Berman has com by his unique opportunities for the study of which this book is the fruit. He matche his splendid opportunities with a diligence and skill which are evident in these pages The scientific value of his observations and deductions have been appraised b Professor Kennaway, and Dr. Berman is to be congratulated upon the high opinio of his work expressed by a leading authority on the problem with which it deals

South Africa offers a potentially rich and promising field for the investigation of a great variety of medical problems of more than local significance. Dr Berman's work is a notable example of what can be achieved by ready perception and enthusiastic exploitation of an opportunity which lay to his hand. I trust that his example will be followed by many other South African medical men, to the advancement of true learning and the fame of their country.

Henry Gluckman,
Minister of Health

Union Buildings,
Pretoria
September, 1947

PRIMARY CARCINOMA OF THE LIVER

CHAPTER I

HISTORICAL

bers Papyrus from Egypt In his studies on cancer, Hippocrates distinguished scirrhus," a hard type of tumour, from open "carcinoma," and has left us classical escriptions of mammary and other forms of external cancer

Cancer of the stomach, uterus and other internal cancers were known to Greek hysicians, but it is evident from their writings that the knowledge was entirely clinical.

If we recognise "scirrhus" as a synonym for cancer, the earliest references to cancer f the liver may then be found in the classic works of the Roman physicians Galen and retæus (second century A.D), who regarded the disease as one of the consequences f "hepatitis"

For almost 2,000 years knowledge of cancer made no appreciable progress until Morgagni (1682–1771) established pathological anatomy as a science of paramount mportance in the study of disease. The foundation of pathological anatomy marks the irst of three stages in the historical development of primary liver cancer; the other two tages coincide with the introduction of histopathology and experimental pathology.

Stage I Pathological Anatomy

By describing certain "steatomata" or "hard" tumours of the liver, Morgagni drew ttention to the prevalence of internal cancer, and gave the first post-mortem descrip-ion of unquestionable cancer of the liver All his liver cancers, however, were metastatic, or he reported growths of the stomach or pancreas co-existing with those in the liver.

Matthew Baillie (1797) extended Morgagni's work by describing "large white ubercles" in the liver and compared these with "scirrhus" in other organs. He was not ble to distinguish between true cancer and other liver diseases, such as tuberculosis

cancer of the tubercles" of

Baillie were true cancers, inasmuch as their pathological structures and general effects were similar to those of cancer of the breast He also demonstrated the frequent

association of liver cancer with cancer in other organs, but considered that the concurrence of cancer in two organs (e.g. stomach and liver) was evidence of a constitutional cancerous diathesis (Long, 1928).

Stage II. Histopathology

The introduction of the improved microscope at the beginning of the nineteenth century resulted in the elucidation of pathological processes, including the histological description of many liver tumours, but for a long time no precise distinctions were made between primary and secondary cancers in the liver. It was left to Virchow, father of

(originating in such organs as the stomach, colon, etc.) and their massive secondary growths in the liver.

Hitherto most cancers of the liver had been regarded as of primary origin, but following Virchow's discoveries a re-orientation ensued. Von Hansemann (1890) demonstrated that the incidence of primary car
low when compared with that of secondary ca
nant tumours of the liver recorded at the Berli
only 4 of these were primary in origin. With Virchow's criteria as a basis, he held that data concerning primary liver cancer before 1870 were not to be relied upon, and even rejected 17 of 19 cases recorded in the classic work of Frerichs (1859).

Modern literature on primary carcinoma of the liver commences with the publication of 2 cases from Algiers by Kelsch and Kiener (1876) and of 4 others described as "adenomas" by Sabourin (1881) These cases, together with some of their own, gave Hanot and Gilbert (1888) an opportunity to classify primary liver cancer into three macroscopic and two microscopic groups The macroscopic groups were: massive cancer, nodular cancer, and cancer with cirrhosis.

In the microscopic classification they substituted the term "epithelioma" for "adenoma," and divided the tumours into "trabecular epithelioma" and "alveolar epithelioma." The former included the cirrhotic group of cancers, the latter the massive and nodular varieties

Van Heukelom (1894) and later Wegelin (1905) introduced the term "adenocarcinoma" for hepatic cancer. Eggel (1901) abandoned the cirrhotic group of Hanot and Gilbert's classification, and added a diffuse, or infiltrating group. Microscopically, he separated the cases into two histological types—"carcinoma solidum" and "carcinoma adenomatosum" On the other hand, Ribbert (1909) designated all his cases as "malignant adenoma."

The modern microscopic classification was first propounded by Yamagiwa (1911). On a histogenetic basis, he divided primary carcinoma of the liver into two groups—"hepatoma" and "cholangioma," names which denote the origin of the cancers from the cells of the hepatic epithelium and from those of intrahepatic bile ducts respectively. In Yamagiwa's classification, however, the terms "hepatoma" and "cholangioma" apply both to malignant and benign tumours. Accordingly, this classification has been

"hepatocellular carcinoma" (cancer derived from liver cells) and "cholangiocellular carcinoma" (malignant tumours arising from small bile ducts lying in the portal tracts at the periphery of the lobule) Some pathologists, however, prefer the terms "malignant hepatoma" and "malignant cholangioma."

The expansion of medical literature from the middle of the nineteenth century onwards has made possible an appreciation of the nature and distribution of new or uncommon diseases. On account of its rarity in Europe and America, primary liver cancer has attracted the interest of investigators throughout the world. In 1901, Eggel was able to collect from the world's literature only 163 reports of this disease. Goldstein brought the number up to 250 cases in 1924. Six years later Herxheimer (1930) was able to compile a total of 600 cases. Charache in 1939 estimated the total as 1,125. To-day the number is well over 2,000.

For many years it was held that malignant disease occurred but rarely among the aboriginal races, but this belief was shattered by the publication of hitherto unobtainable post-mortem statistics from remote parts of the world during the present century. Moreover, these statistics revealed that primary liver cancer is the most frequent visceral cancer affecting the male members of certain indigenous races of Africa and the Orient a finding which has inevitably given rise to the opinion that primary liver cancer is a disease which is governed by racial factors.

In South Africa the study of malignancy as it affects the indigenous races was neglected until comparatively recent years. Bruce-Bayes (1905), in describing a case of primary carcinoma of the liver, was the first to record malignant disease of any sort in the South African Bantu

No further South African contribution to the subject was made until Pirie (1921), of the South African Institute for Medical Research, analysed 153 Bantu cases of malignancy from the pathological material sent for investigation during 1912–1921. He drew attention to the fact that primary liver cancer accounted for 36 out of 91 instances of carcinoma and gave a good description of the pathology.

Stage III. Experimental Pathology

It will be seen that until the early part of the present century investigators were concerned essentially with the pathological aspects of hepatic carcinoma, but with the advent of bacteriology and stimulated no doubt by the discovery of specific microbes responsible for many infections, energetic studies were undertaken in the hope of isolating similar organisms from tumours These efforts met with little success.

The early clinical observations of Percival Pott (1775) on the cancerous effects of soot on the skin of chimney sweeps, and the appreciation a century later by von Volkmann (1875) of the similar effects of lignite tar, next suggested that some cancers in man could be caused by chemical compounds However, it was not until 1916, when Yamagiwa and Itchikawa produced skin cancers in rabbits by the long-continued application of coal-tar, that the chemical approach to the problem was initiated.

This method of cancer research was developed by Kennaway and the staff of the

Research Institute at the Royal Cancer Hospital, London. The use of fluorescence spectroscopy by Mayneord and Hieger led to the discovery of the carcinogenic hydrocarbon, 3:4-benzpyrene, in coal-tar. This in turn led to the synthesis by Cook and his co-workers of many new carcinogenic compounds, and these methods have been adopted in many different countries.

By virtue of its specific effect on the liver, *o*-aminoazotoluene was the first of the carcinogenic azo-compounds which yielded encouraging results in the experimental production of primary liver cancer. This compound is the active fraction of "scarlet red," the therapeutic agent which has for long been used in surgery to stimulate granulation-tissue formation in slowly healing wounds.

Scarlet red, first used experimentally by Fischer as long ago as 1906 in rabbits, produced epithelial outgrowths which simulated cancer, but these always receded. Yamagiwa (1916) also used scarlet red in attempts to produce malignant growths, but he was only able to induce hyperplasia.

Although *o*-aminoazotoluene was identified as the principal component of scarlet red in 1877, its carcinogenic properties remained unknown until 1935, when Sasaki and Yoshida announced their spectacular successes in the production of primary liver cancer in rats. It is noteworthy that this discovery was the first successful induction of cancer in an internal organ by a chemical compound of known composition.

Recent developments in the experimental production of primary liver cancer include the use of more powerful carcinogenic substances, and the discovery that dietary factors have pronounced effects on tumour formation. The influence of diet on experimental tumour production may have a parallel in human liver cancer, since malnutrition is known to be common among the very races noted for their frequency of primary liver cancer.

Already there are numerous potent external agents with proved carcinogenic affinities for the livers of certain experimental animals. No similar substances, however, have yet been isolated for man. More information is therefore necessary concerning the habits, customs, diets and general health conditions of the populations chiefly affected by primary liver cancer. In any such enquiry, South Africa will undoubtedly play a vital role.

PART I

GEOGRAPHICAL AND RACIAL DISTRIBUTION

CHAPTER II

INCIDENCE OF PRIMARY LIVER CANCER

A SURVEY of the world's available statistics indicates that the incidence of primary liver cancer varies strikingly among the different races of mankind: of rare occurrence among the peoples of Western Europe and North America, it is by contrast remarkably common among the inhabitants of Africa and the Orient.

Among Western Races in Europe and in North America.—Primary liver cancer is very rare amongst all Western people, irrespective of whether they live in Europe, America,

TABLE I

SHOWING INCIDENCE OF PRIMARY LIVER CANCER IN EUROPE (AUTOPSY RECORDS)

Country	*Author(s)*	*No of Autopsies*	*Cases of Primary Liver Cancer*	*Per cent. of all Autopsies*
Belgium	Coers and Drochmans (1947)	3,564	22	0 62
England	Hale White (1900), Wheeler (1909); Glynn (1911), Stewart (1931)	31,583	42	0 13
Germany	Mau (1901), Nobiling (1911), Miliecki (1913); Briese (1922), German Society for Cancer Research (1922), Junghanns (1929), Herxheimer (1930)	171,712	191	0 11
Holland	Dijkstra (1925)	2,936	5	0 17
Hungary	Goldzieher and von Bokay (1911)	6,000	18	0 30
Italy	Cantele (1932)	19,008	44	0 23
Switzerland	Saltykow (1912), Bergeret and Roulet (1947)	13,250	39	0 29
	Total	248,053	361	0 14

Africa or elsewhere As will be seen from Tables I and II, the autopsy rate is 0 14 per cent in Europe and 0 27 per cent in America, whilst the percentage frequency to all forms of cancer is 1 2 per cent in Europe and 2 5 per cent. in the United States of America (Tables III and IV)

Among the Bantu Races of Africa.—In a previous publication the author analysed [illegible]

primary liver cancers (Berman, 1935)

TABLE II

SHOWING INCIDENCE OF PRIMARY CARCINOMA OF THE LIVER IN THE UNITED STATES OF AMERICA (AUTOPSY RECORDS)

Locality	*Author(s)*	*No. of Autopsies*	*No. of Primary Carcinoma of the Liver*
Baltimore	[illegible]	26,200	48
Boston	[illegible]	7,706	13
Buffalo	[illegible]	4,400	12
Charleston	[illegible]	2,470	8
Chicago	[illegible]	7,756	40
Detroit	[illegible]	1,087	8
Iowa	Fox and Bartels (1928)	5,100	1
Minnesota	Clawson and Cabot (1923)	1,500	3
Nebraska	Barry and Russum (1931)	1,100	4
New York	Von Glahn and Lamb (1924), McWhorter and Cloud (1930); Gustafson (1937); Peller (1943)	43,359	149
Rochester	Counsellor and McIndoe (1926)	5,976	5
Texas	Hill (1929)	150	3
Vancouver	Strong and Pitts (1930, 1932)	1,828	2
	Total	108,632	296
	Per cent.	100	0 27

TABLE III

SHOWING RELATIVE FREQUENCY OF PRIMARY CARCINOMA OF THE LIVER TO CARCINOMA OF ALL ORGANS IN EUROPE (AUTOPSY RECORDS)

Country	*Author(s)*	*Total No of Carcinoma of all Organs*	*No of Primary Carcinoma of the Liver*	*Per cent*
Belgium	Coers and Drochmans (1947)	702	22	3 13
England	Thomson (1901), Collwell (1905)	3,470	44	1·26
Germany	Fischer (1903), Orth (1909), Nobiling (1911), German Society for Cancer Research (1921–1922); Junghanns (1929); Herxheimer (1930)	16,347	178	1 09
Holland	De Vries (1918), Dijkstra (1925)	2,668	29	1 09
Switzerland	Jasnogrodsky (1907), Saltykow (1912)	1,350	21	1 56
	Total	24,537	294	1 2

TABLE IV

SHOWING RELATIVE FREQUENCY OF PRIMARY CARCINOMA OF THE LIVER TO CARCINOMA OF ALL ORGANS IN THE UNITED STATES OF AMERICA (AUTOPSY RECORDS)

Author(s)	*Total No of Carcinoma of all Organs*	*No of Primary Carcinoma of the Liver*
Levitt and Levy (1938)	2,099	12
Wells (1923)	495	15
McWhorter and Cloud (1930)	770	39
Brines (1933)	105	8
Wilbur, *et al* (1944)	1,632	49
Wheelock (1948)	501	17
Total	5,602	140
Per cent	100	2 5

This extraordinary tumour localisation has not altered to any appreciable extent during the ensuing years. For the eleven years 1934–1944, 556 cases of malignant tumours of all types were recorded: 519 were carcinomas, and of these 441 (or 85 per cent.) were primary liver cancers (Berman, 1950). Thus, for the twenty years 1925–1944, there were altogether 772 cases of carcinoma, of which 670 (or 86 8 per cent.) were primary liver cancers (Fig. 1). All these cases occurred among a migratory Bantu

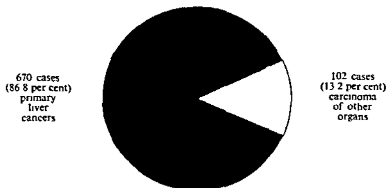


Fig. 1—Showing the relative frequency of primary carcinoma of the liver to carcinoma of all organs in 772 cancer cases found amongst male Bantu labourers on the Witwatersrand gold mines (1925–1944)

population of 200,000 to 300,000 specially selected and fit young adult males, who rarely stayed longer than nine months on any mine and whose ages ranged from 18 to 45, the average being 30 years. They were drawn from the Native Territories of the eastern part of the Union of South Africa and from the adjacent Portuguese African possessions Latterly, too, a small percentage came from Northern Rhodesia and Nyasaland. Consequently, they were representative of most Bantu tribes in southern Africa. Approximately 65 per cent came from the Union of South Africa, Swaziland, Basutoland and Bechuanaland Protectorates ("South African Natives"), and 35 per cent from the Portuguese East African Territories ("East Coast Natives") At the Johannesburg Non-European Hospital during the eight-year period 1926–1933, there were 215 cases of carcinoma, 41 of which were primary carcinomas of the liver. These were observed amongst 41,920 patients of all ages and both sexes (Berman, 1935)

At the Miguel Bombardo Hospital, Lourenço Marques, 85 cases of primary liver cancer were recorded during 1930–1938 amongst a hospital population of 49,000 Bantu patients (Prates, 1943) This high incidence of primary liver cancer is remarkable, for it represents more than double the number of cases seen at the Johannesburg Non-

visceral cancer in Africans It accounted for 19 of 65 carcinoma cases (or 29·2 per cent) autopsied at the Salisbury Native Hospital, and for 25 of 228 carcinomatous tissues (or 10·9 per cent) sectioned at the Salisbury Public Health Laboratory

Of 2,378 tissues from Natives examined at Kenya, Vint (1935) found 277 carcinomata, including 38 (or 13·7 per cent.) primary liver cancers.

Bergeret and Roulet (1947) reported that 35–40 cases of primary liver cancer are treated annually at the Hôpital Central Indigène at Dakar, French West Africa. This form of malignancy, moreover, accounted for 23 per cent. of all cancers in Africans at the Dakar Pathological Institute (Jonchère, 1948).

Available statistics for the Bantu as a whole show that the post-mortem incidence was 1·1 per cent. (Table V), and the relative frequency of primary liver cancer to all

TABLE V

SHOWING THE POST-MORTEM INCIDENCE OF PRIMARY LIVER CANCER AMONG THE BANTU

Source	*Author(s)*	*Number of Autopsies*	*Primary Liver Cancers*	*Per cent.*
City Deep Mine Hospital, Johannesburg, South Africa	Fischer (1929, 1932)	1,963	16	0·8
Non-European Hospital, Johannesburg, South Africa	Strachan (1934)	1,901	37	1 9
Government Hospital, Salisbury, Southern Rhodesia	Gelfand (1947)	2,000	18	0 9
Research Laboratory, Kenya	Vint (1935)	1,100	8	0 7
Mulaga Hospital, Kampala, Uganda	Muwazi, *et al* (1942)	1,104	9	0 8
	Total	8,068	88	1 1

TABLE VI

SHOWING RELATIVE FREQUENCY OF PRIMARY CARCINOMA OF THE LIVER TO CARCINOMA OF ALL ORGANS IN THE BANTU RACES OF AFRICA (PATHOLOGICAL, AUTOPSY, CLINICAL AND OFFICIAL RECORDS)

Locality	*Observer(s)*	*Cases of Carcinoma of all Organs*	*Cases of Primary Carcinoma of the Liver*
Union of South Africa	Pirie (1921), Macfarlane (1924), MacVicar [illegible]	2,565	1,336
Portuguese East Africa	[illegible]	63	23
Kenya	Vint (1935)	16	8
Tanganyika	Official Health Reports (1925)	11	3
Uganda	*Davies (1948)*	85	29
Belgian Congo	Mouchet and Gerard (1919, 1926)	28	15
Fernando Po	Appel (1921)	6	4
French Equatorial Africa	Sumont and Sava (1927)	22	7
	Total	2,796	1,425
	Per cent	100	50 9

other forms of carcinoma was 50 9 per cent (Table VI) Among the semi-*Bantu*, 15 3 per cent. of all cancers were primary liver cancer (Table VII).

Tribal Incidence among the Bantu —Statistics for the Bantu have indicated that there

is an extraordinary tribal difference in incidence of the disease. The Portuguese East African Bantu appear chiefly affected.

An analysis of the 670 cases recorded among the Bantu on the Witwatersrand gold mines during the twenty-year period 1925–1944 shows that 163 (or 24 3 per cent.) were in South African Natives, whereas 507 (or 75·7 per cent) had occurred in Portuguese

TABLE VII

SHOWING RELATIVE FREQUENCY OF PRIMARY CARCINOMA OF THE LIVER TO CARCINOMA OF ALL ORGANS IN THE SEMI-BANTU RACES (OFFICIAL, PATHOLOGICAL AND CLINICAL RECORDS)

Locality	*Observer(s)*	*Cases of Carcinoma of all Organs*	*Cases of Primary Carcinoma of the Liver*
Nigeria	Annual Health Reports (1927); Smith and Elmes (1934), Elmes and Baldwin (1947)	807	119
Sierra Leone	Adler and Cummings (1923)	5	2
Senegal	Nogue (1920)	7	7
Cameroons	Ledentu (1934)	63	7
	Total	882	135
	Per cent	100	15 3

TABLE VIII

SHOWING TRIBAL DISTRIBUTION OF 670 CASES OF PRIMARY CARCINOMA OF THE LIVER AMONGST BANTU LABOURERS OF THE WITWATERSRAND GOLD MINES (1925–1944)

South African Natives			*Portuguese (East Coast) Natives*		
Tribe	*No of Cases*	*Per cent*	*Tribe*	*No of Cases*	*Per cent.*
Xosa	56	34 5	Shangaan	237	46 7
Pondo	22	13 5	Mchopi	136	26 8
Basuto	21	13 0	Nyambaan	79	15 5
Msutu	13	8 0	Tonga	25	5 0
Zulu	12	7 3	Nyasa	3	0 6
Fingo	8	4 9	Barotse	1	0 3
Swazi	8	4 9	Not stated	26	5 1
Hlubi	4	2 4	—	—	—
Baca	3	1 8	—	—	—
Bechuana	2	1 2	—	—	—
Venda	1	0 6	—	—	—
Ndebele	1	0 6	—	—	—
Not stated	12	7 3	—	—	—
Total	163	100 0	Total	507	100 0

East Coast Natives (Table VIII) The average number of Bantu labourers employed per annum over this period was 260,000.

Since approximately 65 per cent of the mine Native population was drawn from the Union of South Africa (including British Protectorates) and 35 per cent from Portuguese East Africa (East Coast Natives), the incidence of the disease was 5 per 100,000 South African Bantu population per annum, and 29 per 100,000 per annum among the Portuguese Natives (Fig 2) Therefore, primary liver cancer occurred 5 8 times more frequently among the Portuguese Natives than among the South African Natives

The reason for this is not obvious. There is no appreciable difference in their general physical characteristics, but geographical and meteorological differences do exist. The altitude of Portuguese East Africa is considerably lower and the climate is moister and more tropical than that of the Union of South Africa. In Portuguese East Africa the crops cultivated are more tropical, and animal proteins and milk are probably less plentiful in those parts of the country where the tsetse-fly is endemic. Intestinal and other parasites may also be more frequent than in South Africa, but definite information on these ætiological factors is not yet available.

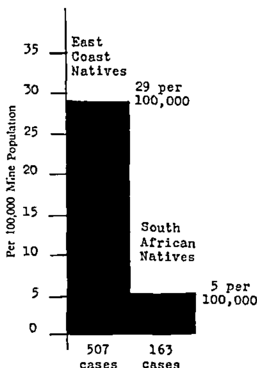


FIG 2.—Comparison of primary liver cancer incidence in East Coast (Portuguese East African) and South African Bantu employed on the Witwatersrand gold mines

With regard to tribal distribution, the Shangaans and the Mchopi showed the highest incidence of the disease among the East Coast Natives (Table VIII); between them they were responsible for 73.5 per cent. of all cases. Among the South African Natives, Xosas ranked highest with 34.5 per cent., followed by Pondos and Basutos with 13·5 and 13 per cent. At the Non-European Hospital, the tribal distribution was more evenly divided, Zulus and Msutus being chiefly affected (Berman, 1940).

The relative frequency of primary liver cancer among the Bantu mine workers on the Witwatersrand is much higher than *among the Bantu population of Johannesburg* and its surroundings. This is to be expected, for as will be seen, primary liver cancer is much more frequent in males than in females, and occurs especially in a young age group such as predominates on the gold mines. In the absence of vital statistics from the South African Native Territories, no definite opinion can be expressed concerning the incidence of the disease for the bulk of the South African Bantu population.

Among Oriental Races.—There must be some factor which is common for the livers of Bantu and Oriental races but is absent or less operative in those of Europeans or North Americans, since among some Oriental people the incidence of primary liver cancer is sometimes as high as in the Bantu.

This is indicated by composite statistics, which show that the autopsy rate is 0.76 per cent. (Table IX), and the relative frequency to all forms of carcinoma is 13·9 per cent. (Table X).

Post-mortem statistics have shown that the liver is the organ of highest cancer frequency in a number of Far-Eastern cities, including Batavia (Bonne, 1937), Singapore (Tull, 1937) and Manila (Vedder, 1927). In Tokyo the liver ranks second as a cancer site, being superseded in this respect by cancer of the stomach (Nagayo, 1933).

TABLE IX

SHOWING INCIDENCE OF PRIMARY CARCINOMA OF THE LIVER AMONG ORIENTAL RACES (AUTOPSY RECORDS)

Race	*Locality*	*Author(s)*	*No of Autopsies*	*Cases of Primary Liver Cancer*	*Per cent*
Chinese	Federated Malay States	Daniels (1908)			
	Sumatra	Snijders and Straub (1923); Kouwenaar (1932)	23,764	215	0 90
	Java	Bonne (1935)			
	Singapore	Tull (1932)			
	Peiping	Wu and Kang (1930)			
	Vancouver	Strong and Pitts (1932)			
Filipinos	Manila	Smith (1926), de Leon (1933)	13,876	61	0·44
Indians	Calcutta	Rogers (1925)			
	Bombay	Gharpure (1927, 1948)	14,768	47	0 32
	Punjab	Nath and Grewal (1935)			
	Madras	Thangavelu (1949)			
Japanese	Kioto	Suzuki (1914)			
	Tokyo	Ishibashi and Takatsu (1915)			
	Kyushu	Yamane (1918)	15,565	151	0 97
	Nugata	Hudimaki (1936)			
	Formosa	Usuda and Uchida (1941)			
Javanese (Malays)	Sumatra	Snijders and Straub (1923), Kouwenaar (1932)	8,253	109	1 31
	Java	Bonne (1935)			
		Total	76,196	583	0 76

TABLE X

SHOWING RELATIVE FREQUENCY OF PRIMARY LIVER CANCER TO CARCINOMA OF ALL ORGANS IN ORIENTAL RACES (POST-MORTEM STATISTICS)

Race	*Locality*	*Author(s)*	*Cases of Carcinoma of all Organs*	*Cases of Primary Liver Cancer*	*Per cent*
Chinese	Hong Kong	Jeffreys and Maxwell (1905)			
	Federated Malay States	Maxwell (1908)			
	Singapore	Snijders and Straub (1923)	456	150	33
	Sumatra	Snijders and Straub (1923), Kouwenaar (1932)			
	Java	Bonne (1937)			
Filipinos	Manila	Smith (1926), de Leon (1933)	275	61	22 2
Indians	Calcutta	Rogers (1925)			
	Bombay	Gharpure (1927, amended 1948)	222	39	17 5
	Punjab	Nath and Grewal (1935)			
	Madras	Thangavelu (1949)			
Japanese	Kioto	Suzuki (1914)			
	Tokyo	Ishibashi and Takatsu (1915), Nagayo (1933)	3,149	249	7 5
	Kyushu	Yamane (1918)			
	Nugata	Hudimaki (1936)			
Javanese (Malays)	Sumatra	Snijders and Straub (1923), Kouwenaar (1932)	262	109	41 6
	Java	Bonne (1937)			
		Total	4,364	608	13 9

The excellent studies by Snijders and Straub (1922, 1923) and other observers in Indonesia have for long indicated that primary liver cancer is by far the most frequent form of carcinoma among Javanese and immigrant Chinese labourers working on tobacco and rubber estates in Sumatra. Indeed, among the Javanese this malignancy occurs almost as readily as in the Bantu mine-workers of the Witwatersrand. Kouwenaar's (1932) autopsy statistics show that primary liver cancer accounted for 79 3 per cent. of all carcinomas among male Javanese, 31·5 per cent among Chinese males and 6·2 per cent. among Javanese females. Bonne (1935) recorded a somewhat similar incidence among the Chinese of Java, who, unlike their compatriots in Sumatra, are for the most part born on that island and have lived there for generations.

The only other available information concerning primary liver cancer in Asia is as follows:

Degorce (1913) recorded 36 cancers of the liver among 444 biopsy carcinoma specimens obtained at operation from Annamites at Hanoi, French Indo-China Bablet (1932), of the Hanoi Pasteur Institute, found 15 such tumours among 448 cancers.

Usuda and Uchida (1941) discovered 14 primary liver cancers among 502 autopsies on Formosans performed at the Taihouku Imperial University Medical School, Formosa, the large island off the Chinese coast. This gives the very high autopsy rate of 2 7 per cent.

At a hospital in Hainan, another large island off southern China, however, Bercovitz (1941) saw only 4 cases of liver cancer among a total of 451 cancers.

In Korea, Yun (1949) found 24 liver cancers among 429 carcinomas, mostly surgical specimens, examined during 1925–1939 at the Graduate School, Seoul National University

Snijders (1933) found 2 cases of hepatocellular cancer among 13 carcinomas obtained at autopsy on Tamils from Colombo, Ceylon In Ceylon, Cooray (1944) saw only 4 primary liver cancers among 1,815 carcinoma biopsy specimens removed at operations

It must be remembered that with the notable exceptions of Indonesia and Japan, there is a dearth of cancer statistics for the greater part of Asia: we still have an incomplete knowledge of cancer distribution among the various races of that continent. This is due possibly to the scarcity of medical centres where routine post-mortems are carried out, and partly to religious restrictions or popular prejudice against autopsies At the largest teaching hospital in Punjab, for example, only 329 autopsies could be performed between 1921 and 1931 (Nath *et al.*, 1933). It would appear, however, that primary liver cancer, like cirrhosis, occurs relatively frequently in some parts of India. Forsyth (1922) was of the opinion that the disease " . . occurs [illegible] I had long noticed the [illegible] " According [illegible] on in South India. in Madras they found 29 such cases as well as 20 cases of secondary cancer and 17 doubtful cases

On the other hand. Dr Khanolkar, of the Tata Memorial Hospital, Bombay, has informed the author that his experience of twenty-five years has led him to conclude that primary liver cancer is not more common in Bombay than in Europe. This opinion

is strengthened by the recent post-mortem statistics of Gharpure (1948) For a better understanding of the incidence of cancer in Asia, more autopsy records are obviously necessary. The vast area and population (over 400 millions) of India and Pakistan provide a diversity of conditions which might cause considerable differences between the various regions.

Australia and New Zealand.—Cancer statistics for the aboriginal races are also scanty. Cleland (1928), in a general survey of disease among the Australian aborigines, found 3 cases of primary liver cancer among 10 cases of carcinoma

For the Maoris of New Zealand, official statistics (1926) for the five years ending

TABLE XI

SHOWING 254 CASES OF PRIMARY LIVER CANCER IN MAMMALS AND BIRDS
(As recorded in the literature)

Author(s)	*Bovine*	*Dog*	*Duck*	*Sheep*	*Cat*	*Wild Mammal*	*Wild Bird*	*Dom Fowl*	*Horse*	*Pig*
Fadyean (1899)	1	3	—	2	—	—	—	—	—	—
Sticker (1902)	4	20	—	5	2	—	—	—	3	1
Trotter (1904, 1905)	120	—	—	—	—	—	—	—	—	—
Murray (1908)	7	—	—	—	—	—	—	—	—	—
Joest and Ernesti (1916)	—	—	—	—	—	—	2	—	—	—
Siedamgrotzky (1916)	—	—	—	—	—	—	—	1	—	—
Fox (1925)	—	—	—	—	—	5	4	—	—	—
Hoogland (1926)	5	10	—	—	3	—	—	—	—	—
Feldman (1928)	2	—	—	—	—	—	—	—	—	—
Behnke (1931)	—	—	—	—	—	—	—	—	1	—
Lombard (1932)	—	—	—	—	—	—	—	1	—	—
Langhof (1932)	1	—	—	—	—	—	—	—	—	—
Montpellier and Dieuzede (1932)	—	—	—	—	1	—	—	—	—	—
Jackson (1936)	9	2	—	4	—	—	—	1	—	1
Feldman (1936)	—	—	—	—	—	—	—	—	—	1
Norris (1936)	—	—	—	—	—	—	—	1	—	—
Kahlau (1937)	—	—	—	—	—	—	—	1	—	—
Winer and Schroeder (1940)	—	—	—	—	—	1	—	—	—	—
Willis (1948)	—	6	—	—	1	—	—	—	—	—
Campbell (1949)	—	—	22	—	—	—	—	—	—	—
Total	149	41	22	11	7	6	6	5	4	3

1924 show 69 deaths from malignant disease (41 males and 28 females). These included 8 cases of primary liver cancer—all in males

Mammals and Birds.—Records of cancer in the lower animal kingdom are not without significance, since the comparative study of tumours may yet prove important in our ultimate understanding of the cancer problem

Primary liver cancer is not unusual in animals, and has even been found in a frog (Willis, 1948) The number of cases reported in the available literature totals 254, mostly in domesticated animals and birds (Table XI) It is noteworthy that this total included 120 cases in aged cattle observed in a single year at a Glasgow abattoir (Trotter, 1904, 1905)

The recent study by Campbell (1949) of hitherto unrecorded primary liver cancers in female ducks of the Khaki Campbell breed deserves special mention Altogether



FIG 3 —Showing geographical areas of known or suspected high primary liver cancer incidence.

22 such cancers were discovered, including 17 hepatocellular, 1 cholangiocellular and 4 mixed tumours. Extrahepatic metastases were found in 10 instances, chiefly in the lungs.

Biopsy fragments of a hepatocellular tumour were successfully cultivated on the chorioalantoic membranes of fertilised eggs, and in the anterior chamber of a guinea-pig's eye. Saline suspensions of the same tumour produced hepatocellular and cholangiocellular cancers respectively when inoculated into the livers of two young ducks of the same breed. There were no metastases.

Biopsy fragments of a mixed tumour implanted into the liver of a third duck developed into a large hepatocellular cancer with metastases in the lungs, kidney and ovary.

CHAPTER III

COMMENT AND SUMMARY OF INCIDENCE

THE foregoing statistics, dating from the early part of the present century, have been derived from every source of cancer literature available to the author. They embrace the majority of primary liver cancers recorded during that period, and constitute as reliable statistical data relative to the disease as are available to-day. It must be remembered, however, that information from certain parts of the world is limited· statistics for South Western Africa and for Central and South America are singularly lacking, and for the whole of India and Pakistan, with a population of more than four hundred millions, only six papers on the subject have been published so far.

The salient features of the present survey are that primary liver cancer is by no means confined to man, and that while it is extraordinarily frequent among native African and Oriental races, it is, on the contrary, very uncommon among the people of the Western nations Geographically, the area of high prevalence extends from the West African coast, along the south-eastern and eastern portions of Africa, across eastern and south-eastern Asia, to and including particularly Indonesia, the Philippines, China and Japan (Fig 3)

PRIMARY LIVER CANCER IN THE BANTU RACES OF AFRICA

Primary liver cancer is the most frequent form of malignancy encountered in Bantu males It was responsible for 86 8 per cent of all cancers in Native mine-workers on the Witwatersrand (Fig 1), and for 31·9 per cent. of cancers in Bantu males treated at the Johannesburg Non-European Hospital, in Bantu females, the incidence was 5 1 per cent carcinoma of the genital system (75 per cent of all cancers) ...

1·1 per cent. of post-mortems (Table V)

In Portuguese East Africa, 85 cases were treated in one hospital during nine years (Prates, 1940) These figures are significant, for the incidence of the disease among similar Africans working on the Witwatersrand gold mines was almost six times that of the South African Bantu (Fig 2).

Records from other parts of the African continent point to a similar high incidence. Table VI demonstrates that in such widely separated territories as Portuguese East Africa, Kenya, Tanganyika, Uganda, Belgian Congo and French Equatorial Africa, the frequency of primary liver cancer to cancer of all organs varies from 33 per cent. to 60 per cent., and is likewise the most frequent form of cancer in males Among West Coast Negroes, classified by Johnston (1922) and Seligman (1930) as semi-Bantu, the disease is also relatively frequent (Table VII).

Primary Liver Cancer among Oriental Races

Cancer statistics for Eastern races are somewhat similar. Despite fluctuations among individual race groups, the relative frequency of primary liver carcinoma to all cancers is 13·9 per cent. (Table X), and the post-mortem incidence is 0 76 per cent. (Table IX)

A detailed analysis shows (Table IX) that in the Javanese (1·31 per cent.) the post-mortem incidence was slightly higher than in the Bantu, and the Japanese figure (0 97 per cent.) almost equalled that for the Bantu. Among Chinese it was 0 9 per cent., Filipinos 0 44 per cent., and Indians 0 32 per cent.

The relative frequency of primary liver cancer to carcinoma of all organs in Javanese males and females (41·6 per cent) and in Chinese (33 per cent.) approximates that for the Bantu; in Javanese males almost 80 per cent. of all carcinomas are primary liver cancers. Among Filipinos and Indians the few available statistics indicate the relative frequency as 22·2 and 17·5 per cent. The Japanese rate is 7·5 per cent. of all cancers, carcinoma of the stomach being the most frequent cancer in males, and carcinoma of the genital system in females. It must be mentioned that gastric cancer is infrequent among both Bantu and Malays. However, according to Nagayo (1933), primary liver cancer ranks third in frequency in males and sixth in females in Japan.

Primary Liver Cancer among People of the Western Nations

Primary carcinoma of the liver is very rare in Europe and America. The post-mortem rate is 0 14 per cent. and 0 27 per cent. (Tables I and II), and for all cancers it is responsible for but 1·2 per cent and 2·5 per cent respectively (Tables III and IV) The organ most frequently affected is the stomach (Hoffman, 1934).

Gnassi (1941), in a survey of 2,870 surgical and post-mortem tumours at Jersey City, found only 4 cases of primary liver cancer, representing 0 1 per cent. of malignancies.

Among Western races living in Africa or Asia, primary liver cancer is as rare as it is in Europe or America. Only 4 such cases were recorded at the Johannesburg General Hospital during the ten years 1925–1934 (Strachan, 1934), and of 114 specimens of primary liver cancer examined by Simson (1936), 4 were from Europeans Among *Eurafricans ("Cape Coloured") Strachan (1934) encountered only 1 case*

Primary Liver Cancer among Oriental and Negro Races in America

Case reports of primary liver cancer in American Negroes and in Chinese, Filipino and Japanese immigrants in America are frequent. In San Francisco, Wilbur *et al* (1944) found that 35 per cent of their cases had occurred in races which comprise a small proportion of the population, including Chinese, Japanese, Filipinos, Ethiopians and Native Americans, and remark "We are impressed by the fact that 19 per cent. of our cases occurred in Chinese."

At the Vancouver General Hospital, Strong and Pitts (1930, 1932) discovered 10 primary liver cancers among 139 autopsies on Chinese; these people are mostly immigrants born in Kwantung province of southern China, and hence the data do not help *us to discriminate between environmental and genetic factors.* During the same period there were only 2 cases of this form of cancer among 1,828 autopsies on white patients

Apparently we have no data for the incidence of primary liver cancer among the large populations of Chinese and Japanese born in North America.

Similarly, in Curaçao, Netherlands West Indies, Hartz (1945) found 5 instances of primary liver cancer in 33 autopsies on Chinese against only 4 instances in 1,350 autopsies on Negro and white subjects.

From the few available post-mortem statistics, however, it will be seen that the incidence of liver cancer among American Negroes, although higher than in Europeans, is very low by comparison with similar statistics from Africa and the Orient.

At the New Orleans Hospital, where almost half the patients treated are Negroes, Boyce and McFetridge (1934) found 28 cases of primary liver cancer, of which 18 were in Negroes. All 6 cases recorded by Lynch (1937) at the Roper Hospital in Charleston, South Carolina (a hospital used almost exclusively by Negroes), were Negro males. These had been found in 1,652 autopsies, of which 1,529 were Negroes

Quinland and Cuff (1940) reviewed 300 cancer cases discovered at post-mortem in Negroes of Tennessee: primary liver cancer was seen three times in 82 males and once in 218 females.

Of 1,817 consecutive autopsies on Negroes in Freedmans' Hospital, Washington, D.C., 12 revealed primary carcinoma of the liver and 166 cancers of all types, giving an autopsy incidence of 0 66 per cent. for primary carcinoma of the liver, and 7·2 per cent. for cancers of all types The ratios in each group were higher than those previously reported in the United States of America and in Europe (Webb, 1945).

Among 2,553 autopsies on Negroes in Panama, mostly from the British West Indies, Tomlinson and Wilson (1945) found 290 carcinomata, including 15 primary liver cancers This gives an autopsy rate of 0 5 per cent. for primary liver cancer and 5 per cent. for cancers of all organs

Kennaway (1944) has collected data upon the incidence of primary liver cancer in *Negroes in the United States. (a) The statistical evidence provided by the United* States Bureau of the Census and by the Metropolitan Life Assurance Company [illegible]

to the percentage of Negroes in the population, which ranges from 0 1 (South Dakota) [illegible]

published cases come leaves no doubt that the Negroes of the "Deep South" are under-represented in the literature, and until we know more about them no exact comparison of the two races in this respect can be made But the figures already available suffice to show that the incidence upon the American Negro is not anything like as high as it is upon the South African Bantu.

From the foregoing, it is clear that there is a marked contrast in incidence of the disease among the different races of mankind Primary carcinoma of the liver, rarely seen among Western people, occurs relatively often and with roughly equal frequency in the African and some Oriental members of the human race Moreover, among Bantu and Javanese males, it is undoubtedly the commonest visceral cancer encountered

Since the disease appears to single out pigmented people, many writers have been inclined to attribute the extraordinary distribution to racial or genetic factors. A discussion on the subject, however, is not relevant at this stage. I have dealt with it elsewhere in this book (see Part IV, Ætiology). My own view, based on experimental and pathological evidence, is that sensitivity to primary liver cancer is due to environmental causes rather than to genetic factors.

Summary of Incidence

1. Primary liver cancer is very rare among all Western people, irrespective of whether they live in Europe, America, Africa or elsewhere. The autopsy rate is 0 14 per cent. in Europe and 0 27 per cent. in America. The percentage frequency to all forms of cancer is 1·2 per cent. in Europe and 2·5 per cent. in America.

2. On the other hand, primary liver cancer is relatively common among the Bantu races of Africa and among certain Oriental races, in some of whom it is more than forty times as frequent as in Western people. The autopsy rate for the Bantu is 1·1 per cent., and 0·76 per cent. for the Oriental races.

3. Among Oriental races the post-mortem rate is as follows: Javanese (Malays), 1·31 per cent.; Japanese, 0·97 per cent.; Chinese, 0 9 per cent.; Filipinos, 0 44 per cent.; Indians, 0 32 per cent.

4. The percentage frequency of primary liver cancer to all other forms of carcinoma is as follows·

(*a*) Among all Bantu races of Africa, 50 9 per cent.; among the young male Bantu employed on the Witwatersrand gold mines, 86 8 per cent ; in Bantu females, 5·1 per cent., among semi-Bantu, 15·3 per cent (*b*) Among all Oriental races, 13·9 per cent.; among Javanese (males and females), 41 6 per cent.: males only, 79 3 per cent.: females only, 6 2 per cent.; among Chinese, 33 per cent ; among Filipinos, 22·2 per cent.; among Indians, 17·5 per cent.; among Japanese, 7·5 per cent.

5 Primary liver cancer is almost six times more frequent in the East Coast (Portuguese East African) Bantu than in the South African Bantu

6. The Chinese immigrants in Sumatra, and (according to isolated accounts) in some parts of the Western Hemisphere, as well as Chinese born in Java, show a high incidence of the disease.

7. The incidence of the disease among American Negroes, although higher than in Europeans, is very low by comparison with Africans and Orientals

8. Over 250 cases of primary liver cancer have been reported in mammals and birds.

PART II

CLINICAL MANIFESTATIONS

CHAPTER IV

GENERAL ÆTIOLOGY CLINICAL CLASSIFICATION TYPICAL CARCINOMA OF THE LIVER — GROUP I: FRANK CANCER

GENERAL ÆTIOLOGY

Sex.—Primary liver cancer is predominantly a disease of males Of 163 cases analysed

(1939), and 47 of the 49 recorded by Wilbur *et al.* (1944). Among 134 Chinese cases all but 1 were males (Tull, 1932).

For the Bantu, all 670 cases recorded on the Witwatersrand gold mines were men (it must, of course, be remembered that the whole Native mining population is male) Of the 41 cases treated at the Johannesburg Non-European Hospital, 36 were males; 80 of 85 cases in Portuguese East Africa (Prates, 1940), and 28 of 29 cases in Uganda (Davies, 1948) were males

TABLE XII

SHOWING AGE DISTRIBUTION OF PRIMARY CARCINOMA OF THE LIVER IN 443 BANTU CASES (1925–1944)

Years	No of Cases	Per cent
11-20	23	5 2
21-30	210	47 4
31-40	152	34 3
41-50	46	10 4
51-60	11	2 5
61-70	1	0 2
Total	443	100 0

Age —No age is exempt from primary liver cancer; it is even found in very young

the decennium 21 to 30 years (Table XII).

In Europe, America, Japan and elsewhere the disease is very rare before 40 years, the majority of cases occurring in the fifth and sixth decades (Eggel, 1901, Yamagiwa, 1911).

Primary Liver Cancer in Childhood.—Primary liver cancer has been encountered in children of all ages. Noeggerath (1854) observed a case in a newborn child. Widenhofer, and Wilbur *et al* (1944), each reported a case in a three-day-old child. In the latter there was already a metastatic growth in the arm. Wollstein and Mixsell (1919) described the condition in a baby aged 4 months.

Dansie (1922) found records of 23 cases in children under 2½ years, whilst other investigators—including Philipp (1907), Castle (1914), Griffith (1918), Kilfoy and Terry (1929), Pirie (1932), and Platou and Hill (1942)—have at different times tabulated and discussed similar cases in older children.

Herxheimer (1930) was able to find 44 descriptions of cases in children under 10 years of age. Steiner (1938) reviewed 105 cases in children under 16 years, of which 75 presented definite evidence justifying the diagnosis In 1942 Tomlinson and Wolff brought the total to 82 cases. To date there are almost 100 such reports in the literature. The youngest case thus far observed in the Bantu was a child aged 10 (Pirie, 1921)

Heredity.—Observations by Slye (1916), Pybus and Miller (1942) and other geneticists on the inheritability of spontaneous tumours in mice, have suggested that hereditary factors may explain the striking differences in the distribution of primary liver cancer in man This theory, however, has not been proved

The only connection between heredity and primary liver cancer thus far claimed was a report by Hedinger (1915), who found the disease in two sisters aged 71 and 77 years.

Trauma.—A previous history of trauma is most unusual. I have found only four instances in the literature where malignancy was believed to have been precipitated by an abdominal injury

Acland and Dudgeon's (1902) case had received three blows on the abdomen fifteen months before the onset of his illness. Hicks (1929) recorded a case with a history of trauma over the liver region, but this had occurred five years previously. Crawford's (1931) patient had received a blow on the abdomen six weeks before admission to hospital. Calcagni (1933) stated that his case had been struck in the right hypochondrium, and died five months later from primary liver cancer. In all these cases, however, the trauma may have been fortuitous

Cholelithiasis.—A possible relationship between gall-stones and primary liver cancer has been suggested by Sanes and MacCullum (1942), who reported 2 cases of cholangioma associated with cholelithiasis, and quoted only two others from the literature.

Cholelithiasis is very rare in the Bantu (Lopis, 1947) I have seen no cases of primary liver cancer associated with cholelithiasis.

CLINICAL CLASSIFICATION INTO FIVE GROUPS

One Typical (Group I). Four Atypical (Groups II to V)

A study of 75 Bantu cases of primary liver cancer has indicated that the clinical course of the disease is by no means uniform Symptomatology is dependent upon three factors rate of growth, complications and metastases. For practical purposes I have divided my cases into five clinical groups (one typical, four atypical) as follows:

Group I Frank cancer i e where the symptoms indicate primary liver involvement (47 cases, or 62 7 per cent of the total)

Group II. Acute abdominal cancer: where the symptoms are associated with an acute abdominal catastrophe (6 cases, or 8 per cent of the total).

Group III. Febrile cancer: i e where fever is the salient clinical feature (6 cases, or 8 per cent. of the total).

Group IV. Occult cancer: in these cases malignancy is discovered accidentally (12 cases, or 16 per cent. of the total).

Group V. Metastatic cancer: here the symptoms are referable to the organs involved by metastases rather than the liver (4 cases, or 5·3 per cent of the total)

I have found this classification equally satisfactory for the cases of primary liver cancer recorded in the literature.

TYPICAL CARCINOMA OF THE LIVER

GROUP I—FRANK CANCER

(62 7 per cent of cases)

In this group are included cases where the signs and symptoms are referred to the liver from the beginning in patients previously in good health. This type of cancer, too, is the one in which a correct diagnosis can be made with confidence.

The most striking clinical findings are asthenia, loss of weight, abdominal pain and tenderness, and enlargement of the liver Less frequent signs are anæmia, jaundice, ascites, peripheral œdema, dilatation of the superficial abdominal veins, dyspnœa and hæmatemesis.

Mode of Onset —Usually no outstanding subjective signs are encountered in the early stages, for the disease makes steady, silent progress over an indefinite period. On this account patients may be ignorant of their ailment until the cancer has reached alarming dimensions

The prodromal symptoms are vague and indefinite, and are attributed to gastric disturbances, e g lack of appetite. Nausea and intermittent vomiting was experienced in 19 per cent of my cases. Although constipation is the rule, in 12 per cent. of my cases diarrhœa occurred In rare instances there may be abdominal pressure and a sense of fullness in the upper abdomen, principally after meals. Only 25 per cent of my cases had any symptoms within three months of their first reporting ill. The majority dated the onset of the disease six to thirty days before admission to hospital.

SYMPTOMS

A study of the pathology has revealed two separate lesions in primary carcinoma of the liver, namely, cancerous infiltration and cirrhosis These factors, taken collectively, have a direct bearing on the clinical picture now following, as each is responsible for well-defined clinical signs Thus asthenia, loss of weight, emaciation and anæmia are due to general constitutional disturbances commonly associated with malignant disease Liver enlargement, tenderness and jaundice are the direct effects of carcinomatous infiltration; and ascites, dilatation of the superficial abdominal veins, œdema and hæmatemesis are the results of cirrhosis

Asthenia.—Loss of strength is one of the most constant features and occurred in 86 per cent of my patients Although mining, the occupation of most of my cases,

calls for sustained physical effort, weakness was usually first experienced only a few days before admission to hospital. Thereafter, it progressed so rapidly that they found themselves unable to perform their work. It was this symptom which usually forced them to seek medical treatment. The late onset of asthenia is remarkable because autopsy not long afterwards often revealed extensive carcinomatosis involving major portions of the liver, apparently of long duration.

Asthenia *may be due to diminished metabolism of the liver, to toxic products* arising from necrosis of tumour tissue, and possibly to secretions originating in the tumour cells.

Abdominal Pain.—Pain occurs in more than 90 per cent. of cases It is of a dull, aching character localised to the right hypochondrium Not infrequently it is referred to the back. Pain, though constantly present, is more marked on exertion. It has no relationship to meals With advance of the disease, the pain increases in severity.

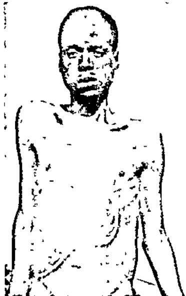


FIG 4 —Primary liver cancer in a Bantu aged 24 The enlarged liver has been outlined This patient died less than two weeks after the photograph was taken

Severe pain is due to perihepatitis or to rapid stretching of the liver capsule resulting from sudden increase in growth of the tumour mass The most excruciating pain is experienced when the tumour spreads to the diaphragm. Where pain is absent or only slight, the growth is usually deep-seated.

Dyspnœa.—Breathlessness, especially on exertion, was present in 25 per cent of my cases. It was usually a late symptom, and was most marked in cases with ascites, anæmia, cachexia and pulmonary metastases.

Pruritus.—Pruritus has been mentioned by some observers as being intense in primary liver cancer. I have not found this the case in any of my patients.

PHYSICAL SIGNS

Cachexia and Emaciation.—A loss of weight and flesh is most common, and occurred in 83 per cent. of my cases.

In the earlier stages, however, even when nodular enlargement of the liver can be felt, there may be little to note in the patient's appearance. The general condition is good, and in many cases may remain so during the greater part of the illness, but with advancing disease the weight rapidly decreases and a condition of cachexia sets in. The eyes become sunken, the cheeks and temples fall in, the features become pinched and the face hollow and haggard. The skin is rendered inelastic by the absorption of fat.

was 3,960 grm. The right lobe of the liver enlarges most frequently. The heaviest liver

encountered thus far, 24 lb. or 10,896 grm, was recorded by Cooper-Cole *et al.* (1935)

The lower outline of the liver may be visible as well as palpable, and its edge is found to be firm, hard and irregular. Very large masses occasionally appear to be fluctuant. The extent of the enlargement usually varies from 2 to 4 inches below the right costal margin, to the level of the umbilicus. In one of my cases it was felt in the epigastrium only. The liver mass may occasionally reach far below the level of the umbilicus; in two of my cases practically the whole right side of the abdomen was occupied by the tumour (Figs. 4-6).



Fig. 5 Fig 6

Figs. 5 and 6—A Bantu case of primary liver cancer The lower outline of the liver is below the umbilicus, which is protruding Note the marked ascites, dilated abdominal veins, œdema of the lower extremities and atrophy of the thoracic muscles

Upward enlargement, resulting in compression of the base of the right lung, occurs less frequently, and was noted by the author in only 13 cases, in the majority of whom the upper margin of the liver was found at the level of the fourth rib. A radiological feature was fixity of the diaphragm.

Irregularity of the liver edge is due to the presence of carcinomatous nodules. These occasionally become softened as the result of necrobiosis, and on palpation a feeling suggestive of fluctuation is elicited. Tenderness is then a marked feature.

Tenderness of the Liver.—The liver is tender to palpation in 90 per cent. of cases The degree of tenderness varies considerably in individual patients. In deep-seated tumours and in the early stages of the disease it is mild, but in cases with nodular formation, with perihepatitis and in terminal stages of the disease, tenderness may become so pronounced as to render palpation of the liver difficult

Jaundice.—Jaundice is a variable sign despite extensive and at times almost total destruction of normal liver tissue. Eggel (1901) found jaundice in 61 per cent. of cases; Tull (1932) in 34 per cent.; Smith (1933) in 72 per cent, and Wilbur *et al.* (1944) in 60 per cent. of cases In my series it was present in 45 per cent. of cases, and always appeared late in the progress of the disease.

It is usually first noticed in the conjunctivæ eleven to twelve days before death The mucous membranes of the lips and palate are affected later It is mild to moderate in degree, being pronounced in exceptional cases only, but once it has appeared its progress is rapid.

The degree of carcinomatous infiltration appears to have little relationship to the incidence of jaundice. This is remarkable, for a large number of cases have been observed at autopsy where, although the liver was almost totally replaced by new-growth, jaundice was either absent or only mild in degree.

Where jaundice is present the icteric index is always raised. In my series of cases it

varied from 7 to 60 units. The highest icteric index was found in a case with the slowest-growing tumour. This patient was in hospital for over four months.

The van den Bergh Test is not uniform Some cases yield a "prompt direct" result, others a "delayed direct," some an "indirect" and others even a "biphasic" result. In a recent case the van den Bergh reaction was seen to change as the disease progressed. On admission to hospital it was negative. Six weeks later it was "positive indirect,"

TABLE XIII

BLOOD PICTURE IN 21 BANTU CASES OF PRIMARY CARCINOMA OF THE LIVER

Case No	*Hæmoglobin, per cent.*	*Colour Index*	*Red-blood corpuscles (millions per c mm)*	*Anisocytosis*	*Poikilocytosis*	*Polychromasia*	*Leucocytes (thousands per c mm)*	*Polymorphs, per cent*	*Monocytes, per cent*	*Lymphocytes, per cent*	*Mast Cells, per cent*	*Eosinophiles, per cent*
16	66	0.88	3.75	+	−	+	6.6	69.0	4.0	26.0	0.0	1·0
22	80	1.01	4.32	−	−	−	8.0	64.5	1.0	29.5	0.0	5.0
24	82	1.1	4.15	+	+	−	9.0	73.5	0.0	26.5	0.0	0.0
25	90	0.81	6.13	−	−	−	8.2	72.5	1.0	20.5	0.5	5.5
26	66	0.8	3.06	+	−	+	6.6	77.0	5.0	18.0	0.0	0.0
38	60	0.9	3.84	−	−	−	9.8	61.0	1.0	37.0	1.0	0.0
40	78	1.1	4.12	−	−	−	7.4	53.0	1.0	46.0	0.0	0.0
42	20	0.6	1·5	+	+	+	14.8	69.0	0.0	27.0	0.0	4.0
43	64	0.9	4.24	+	−	+	14.2	48.0	0.5	47.5	0.0	4.0
44	57	0.63	4.68	−	−	−	7.8	70.5	0.0	28.0	0.0	1.5
45	75	0.88	5.09	+	+	+	5.4	80.0	3.0	17.0	0.0	0.0
51.	66	0.88	3.75	+	−	+	6·6	69.0	4.0	26.0	1.0	0.0
53	62	0.8	4.88	−	−	−	11.8	63.0	1.0	34.0	0.0	2.0
58	90	0.89	5.8	−	−	−	11.6	63.0	3.0	34.0	0.0	0.0
63	70	0.94	4.11	−	−	−	10.2	59.0	0.0	38.0	1.0	2.0
65	80	0.95	4.67	−	−	−	10.0	61.0	3.0	35.0	0.0	1.0
68	76	0.77	4.96	−	−	−	7.5	66.0	3.0	24.0	0.0	7.0
70	90	0.97	5.53	−	−	−	7.5	55.0	5.5	35.5	1.0	3.5
72	76	0.52	4.12	−	−	−	11.6	78.0	8.0	13.0	0.0	1.0
74	69	0.91	4.34	−	+	−	8.2	55.0	6.5	26.5	0.5	11.5
75	58	0.86	4.14	−	−	+	7.8	49.5	4.5	43.0	0.0	2.5

whilst twenty-five days afterwards (or seven days before death) it yielded a "weak biphasic" reaction

Ascites.—Accumulation of serous fluid in the general peritoneal cavity is frequent Eggel (1901) found it in 58.5 per cent of cases, Tull (1932) in 47 per cent., Smith (1933) in 72 per cent., and Wilbur *et al* (1944) in 60 per cent. of cases In my own series it was present in 55 per cent. of cases.

The appearance of the abdomen depends upon the quantity of fluid present Those patients who live longest present a gradual uniform enlargement of the abdomen. The appearance of the patient is then characteristic The atrophied thoracic muscles show up the bony skeleton in marked contrast to the swollen abdomen In the more advanced cases of ascites the umbilicus protrudes (Figs 5 and 6) Shifting dullness and a fluid thrill are always obtained Ascites appears relatively early, it was already evident in the majority of my cases at the time of admission to hospital.

The quantity of ascitic fluid varies considerably, but in many cases it may be so

great that the abdomen becomes tense and glistening Ascites may interfere with respiration, and the heart action may be embarrassed Repeated paracentesis is then [illegible]

from a ruptured nodule on the surface of the liver), or bile-stained. It is alkaline, with a specific gravity not higher than 1 023. It does not coagulate spontaneously and contains no sediment, nor does it contain mucin, nucleo-protein or sugar The albumin content is increased. Microscopic examination may reveal lymphocytes, mononuclear leucocytes, endothelial cells and erythrocytes. Polymorphonuclear leucocytes are occasionally seen. Carcinoma cells were not observed by the author, and cultivation for micro-organisms yielded negative results

Ascites is due mainly to obstruction of the portal circulation, either as the result of the associated cirrhosis, pressure by metastatic glandular enlargements outside the liver, or cancerous infiltration of the sinusoids (Fig 44), thereby setting up venous stagnation and cancerous thrombosis. In many advanced cases thrombosis has been observed to spread along the inferior vena cava and even into the heart (Counsellor and McIndoe, 1927; Culpepper and Von Haam, 1934). Thrombosis of the portal vein was the immediate cause of death in the case described by Liesch (1931).

Splenomegaly.—The spleen is usually enlarged from three to four finger-breadths below the left costal margin, and is of firm consistence. In my series of cases the smallest spleen weighed 200 grm , the largest 900 grm , the average 400 grm.

In tropical countries, however, where malaria is endemic, splenomegaly is of common occurrence in the average population, and is therefore of no special diagnostic significance for primary liver cancer.

Venous Hum.—A humming sound or murmur may occasionally be heard on auscultating the liver tumour This sign was noted in only one of my cases, which proved to be the largest tumour of my series. It is possibly due to excessive vascularity of the growth, or to constriction of the inferior vena cava.

Anæmia.—Progressive blood changes indicative of secondary anæmia are constantly found in the late stages of primary liver cancer Table XIII shows the peripheral blood picture in 21 Bantu cases.

From this table it will be seen that the hæmoglobin content was diminished in every case. The percentage hæmoglobin varied between 20 and 90, the average being 75 The colour index, with the exception of 3 cases, was below 1 The erythrocyte count was noticeably diminished, in one case (No 42) it was 1,500,000 per c mm The leucocyte count varied from normal to a moderate leucocytosis. A lymphocytosis of over 30 per cent occurred in 9 cases. The character of the red-blood corpuscles appears to be altered to a marked degree in some instances *anisocytosis* was present in 10 cases, poikilocytosis in 5, and polychromasia in 8 cases. Hypochromasia was observed in several cases Eosinophilia was associated with parasitic infestation of the alimentary tract

Dilatation of the Superficial Abdominal Veins.—A sign of lesser frequency in primary liver cancer is prominence of dilated abdominal veins This was noticed in 19 per cent. of my cases, in all of whom the veins became visible only late in the course of the

disease. Smith (1933) found this sign in 32 per cent. of cases and Tull (1932) described it in 52 per cent. of cases.

In most instances the veins affected are above the level of the umbilicus. Rarely, large tortuous veins may be seen extending over the whole abdominal wall. Venous distension may be caused by excessive weight of an enlarged liver, by an attempt on the part of the venous system towards the establishment of a collateral circulation, or by compression of the inferior vena cava by ascitic fluid.

Peripheral Œdema.—Œdema, varying from slight puffiness around the ankles to well-marked swelling of the feet and legs, occurred in 30 per cent. of my cases, and was also a late manifestation (Fig. 5). Eggel (1901), Tull (1932), and Wilbur *et al.* (1944), noted œdema in 41 per cent, 83 per cent., and 42·5 per cent. of cases respectively.

Œdema is mainly due to obstruction of the inferior vena cava by pressure of an enlarged liver, portal lymph glands, ascitic fluid or tumour thrombosis. It may also result from anæmia, hepatic insufficiency and toxæmia, or terminal cardiac debility.

Hæmatemesis.—Where there is marked obstruction in the portal system, dangerous hæmatemesis may occur. Hæmatemesis is a rare complication, and occurred twice in my series of cases. Both were cases of primary liver cancer with marked cirrhosis, one of whom was already moribund when admitted to hospital, the other died two days after admission. Autopsy revealed the immediate cause of death to have been hæmorrhage from rupture of large varices at the lower end of the œsophagus. Muir (1908) has described a similar case.

Coers and Drochmans (1947) recorded 2 cases where rupture of a varix in the stomach precipitated the fatal outcome.

Gynæcomastia and Testicular Atrophy.—As in other chronic liver diseases (Glass *et al.*, 1940), including cirrhosis associated with malnutrition (Klatskin, 1947), varying degrees of gynæcomastia and testicular atrophy may be observed in cases of primary liver cancer; such changes were not conspicuous in any of my cases, but no histological examinations nor hormone assays were made. Bernstein (1948) described a case in a young man where these signs were conspicuous. Gynæcomastia and testicular atrophy are regarded as manifestations of disturbed œstrogen metabolism

Temperature and Pulse.—Although the temperature usually remains normal, an intermittent irregular fever of short duration was observed in 38 per cent. of my cases, when the maximum temperatures attained were: 103° F (4 cases), 102° F. (1 case), 101° F (4 cases), and 100° F (9 cases). Terminal rises of temperature to 105° F. may occur. Fever may be caused by necrosis of tumour tissue (Figs. 50 and 51).

The pulse rate was raised in 62 per cent. of cases, the rate varying between 90 and 120 per minute, and was observed even in cases without fever. The blood-pressure usually remained within the bounds of normal.

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and

The stools are often bulky, clay-coloured and offensive

CHAPTER V

ATYPICAL PRIMARY LIVER CANCER

(GROUPS II–V)

THE characteristic feature of all these cases is that the original tumour in the liver usually remains symptomless. The first inkling of the disease may be the occurrence of a grave complication At other times, the patient's complaints are referred entirely to the site of a distant metastasis The primary liver tumour is often found only by accident Moreover, there are some cases in whom the clinical course is so rapid that malignancy is not even suspected.

GROUP II—ACUTE ABDOMINAL CANCER

(8 per cent. of cases)

These are latent cases of primary liver cancer which suddenly develop signs and symptoms pointing to an acute abdominal catastrophe following rupture of a carcinomatous nodule or erosion of a blood-vessel on the free surface of the liver.

Signs and Symptoms.—Immediately prior to admission to hospital, these cases apparently enjoy good health and are often at work. Suddenly they develop signs and symptoms pointing to an acute abdominal catastrophe. A history of trauma is rare, but abnormal muscular exertion preceding the onset of symptoms may occasionally precipitate rupture of a latent cancerous nodule. Intraperitoneal hæmorrhage ensues,

A definite diagnosis, in these circumstances, is extremely difficult. The condition is usually mistaken for perforated gastric or duodenal ulcer or volvulus Laparotomy is imperative

Findings on Abdominal Section.—When the abdomen is opened, the peritoneal cavity is found filled with free and partly coagulated blood The liver is seen to be the seat of numerous carcinomatous nodules, some of which show signs of degeneration. The source of bleeding is located to a nodule which has eroded the liver capsule or a superficial blood-vessel Bleeding is sometimes so severe and continuous that it can be controlled only by gauze packing.

Clinical Course.—Among my own series of 6 cases, 2 died shortly after admission to hospital, before operative treatment was possible Two others died one day after admission to hospital: operation was out of the question in 1 patient, as he was already

in extremis, whilst the general condition of the other was hopeless, for laparotomy revealed the peritoneal cavity to be completely filled with blood

The remaining 2 cases survived operation by less than forty days. Before death they developed signs and symptoms of "typical" primary liver cancer, including jaundice and cachexia. There was intermittent pyrexia. Small recurrent hæmorrhages from the laparotomy opening and a blood-stained discharge persisted till the end.

One of my patients succumbed to hæmorrhage from spontaneous rupture of a tumour nodule some time after he had been diagnosed as primary liver cancer. This occurred in a young Bantu miner who was awaiting repatriation to his native home. A somewhat similar case has been reported by Schnabel (1935). His patient, a Chinese, died suddenly while being investigated for enlargement of the liver. Autopsy revealed blood in the peritoneum secondary to a ruptured nodule in primary liver cancer.

Review of the Literature.—Abdominal disasters due to hæmorrhage from cancerous livers have been recorded by Weber (1910); Pirie (1921), 2 cases amongst the Bantu; Sala (1927); Strong and Pitts (1930), 3 cases in Chinese; Neuffer (1931); Rosenthal (1932); Mast and Streamer (1932); Armand de Lille *et al* (1934); Boyce and McFetridge (1934), 2 cases; Schnabel (1935); Loeper (1937); Lynch (1937); Trizzino (1938). Busser *et al.* (1939); Jenks *et al* (1939); Gustafson (1939), 3 cases; Bunch (1943); Young (1944), Warvi (1945); Schiff (1946).

Tull (1932) found only 1 case among 134 recorded liver cancers in Chinese. Bonne (1932), however, encountered numerous fatal hæmorrhages among Javanese and Chinese in Indonesia, usually from nodules in small cirrhotic livers.

Exceedingly diffuse replacement of liver by tumour tissue may, rarely, produce a hepatorenal syndrome. Schiff (1946) described such a syndrome in two patients in whom the hepatoma was accompanied by stupor, oliguria, azotæmia, deep jaundice and coma.

CHAPTER VI

GROUP III—FEBRILE CANCER

(8 per cent of cases)

THESE are cases of rapidly growing liver tumours with clinical manifestations resembling tropical liver abscess.

Mode of Onset.—As a rule the disease is ushered in suddenly. The patient, previously in good health, suddenly complains of severe pain and tenderness in the liver region accompanied by fever and toxæmia.

Not infrequently, the onset is more insidious for the patient, having been aware of a slowly growing, symptomless tumour in the right hypochondrium over a considerable period, suddenly experiences an acute attack of pain and tenderness accompanied by a more rapid enlargement of the tumour, together with febrile and toxic symptoms. There were 2 such cases in my series, one dating the liver enlargement three months, the other two months, before the onset of acute symptoms

Signs and Symptoms.—The most important sign in this group is pyrexia. The temperature, usually irregular, may rise to 103° F Sometimes it is characteristically hectic, there being wide excursions between the morning and evening temperatures The pulse rate may rise to 120 per minute Rigors were not seen in my cases. There may be a moderate leucocytosis, but eosinophilia is not marked There is great thirst and the tongue is dry The urine may be scanty and highly coloured. In the later stages of the disease bile may be present Vomiting does not occur.

The liver is enlarged, smooth, frequently nodular, and invariably tender to palpation. There is pain in the hepatic region, at first only amounting to a dull ache or a feeling [illegible]

marked jaundice developed in one instance

Diagnosis from Amœbic Liver Abscess.—The clinical manifestations are thus closely similar to those of amœbic abscess of the liver, for which condition this type of cancer is invariably mistaken, more particularly as infection with *Entamœba histolytica* is relatively frequent in South Africa

Differentiation between the two diseases is often difficult, but the finding of the responsible parasite in the stools or the aspiration of pus from the liver helps in establishing the diagnosis The clinical signs, however, may be so similar that the diagnosis may not be effected even on abdominal section This was seen in one of my cases in whom several "abscesses" were located in the liver. These were incised and a purulent material exuded It was only after scrapings from the abscess wall had been examined histologically that its cancerous nature was revealed

Clinical Course.—The most virulent as well as the most rapidly growing of all primary liver cancers are to be found in this group

Of the 6 cases studied by me, 2 died within three days of admission to hospital, and 3 others were operated upon with the object of draining what was thought to be a liver abscess, but none survived the operation by more than eight days or lived longer than twenty-one days after admission to hospital.

Review of the Literature.—Cases of primary liver cancer simulating abscess of the liver have been recorded by: Acland and Dudgeon (1902); Marshall (1915); Snijders and Straub (1923); Trabaud (1924); Colella (1927); Nordman (1927); Bonne (1932); Viannay *et al.* (1932); Laporte *et al.* (1933); Molinari (1933); Pruys (1941); Massias *et al* (1948)

In the case described by Schlomowitz and Glickman (1934), primary liver cancer was mistaken for empyema of the gall-bladder.

Bonne (1932) stated that this type of liver cancer is relatively common in Sumatra, where it is also nearly always misdiagnosed and treated as liver abscess.

CHAPTER VII

GROUP IV—OCCULT CANCER

(16 per cent. of cases)

In this group may be conveniently placed those latent cases of primary liver cancer which are discovered either during examinations for complaints other than those attributable to liver disease, or are accidentally found at autopsy.

Cases Discovered Accidentally.—In my own series there were 12 such cases. Five of these were diagnosed only after admission to hospital and whilst undergoing treatment for bronchitis (2 cases), influenza, dysentery or a knee injury. In 7 others the disease was discovered at autopsy; these were in cases treated for pneumonia (6 cases) and acute nephritis (1 case).

Review of the Literature.—Of 4 latent primary liver cancer cases recorded by Pirie (1921), one was in a Bantu mine labourer who had died of pneumococcal meningitis, and the remainder were discovered in patients treated for scabies, scurvy or dysentery.

[illegible]

coma due to excessive liver destruction.

The case presented by Mallory (1936) was operated upon for a suspected mediastinal tumour, which proved to be a primary liver cancer pushing the diaphragm high into the thoracic cavity. Six of the 62 primary liver cancers analysed by Gustafson (1937) were in patients whose signs and symptoms did not point to pathological changes in the liver, whilst 7 others died before any diagnosis was possible.

Wood (1938) described a case of generalised xanthomatosis associated with primary liver cancer in an infant

Hansen *et al* (1940) reported a case of primary liver cancer in a child in which marked lipæmia was associated with osteoporosis and gross bony deformity. The authors attributed the osteoporosis to defective retention of calcium and phosphorus by the osseous system as a consequence of impaired liver function

Primary carcinoma of the liver was an incidental finding at autopsy in the 2 cases recorded by Sanes and MacCallum (1942).

The case described by Clayman (1945) was undergoing treatment for diabetes, pulmonary tuberculosis and tuberculous empyema. It was only shortly before death that symptoms pointing to liver disease were first noticed Primary liver cancer, apparently of long standing, was discovered at post-mortem. A similar case was described by Joynt (1944).

Beynon (1948) reported a case of primary liver cancer which was detected by a mass radiography unit in a 15-year-old schoolboy Radiography showed two clearly defined tumours in the lower lobe of the right lung On clinical examination an apparently malignant tumour of the liver was found. Aspiration biopsy confirmed the diagnosis The boy led a normal, symptomless life for one year, but then his condition deteriorated rapidly, and he died sixteen months after the original radiograph.

CHAPTER VIII

GROUP V—METASTATIC CANCER

(5·3 per cent. of cases)

THESE are cases of primary liver cancer in whom symptoms due to metastases in remote organs completely overshadow the primary lesion in the liver, and may even be the only manifestations of otherwise symptomless or unsuspected liver cancer

AUTHOR'S CASES

Case with Pulmonary Metastases.—A Bantu mine labourer 26 years of age complained of cough, expectoration of blood and dyspnœa Clinical examination suggested pulmonary tuberculosis, but a skiagram of the lungs (Fig. 7) gave rise to a suspicion of carcinoma Repeated sputum examinations showed no bacilli. He died eleven days

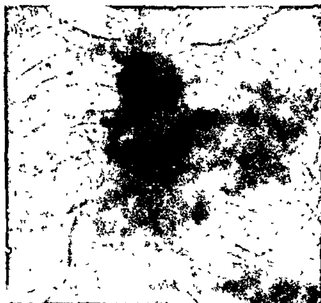


FIG 7—X-ray photograph of the chest, showing metastatic formations in both lungs in a case of primary liver cancer which simulated pulmonary tuberculosis

after admission to hospital Post-mortem examination revealed primary carcinoma of the liver with marked secondary deposits in the lungs.

Case with Metastases in Ribs.—A 24-year-old Bantu complained of a swelling in the right side of the chest which was diagnosed as a lipoma On attempting to excise the growth a highly vascular tumour arising from the ribs was encountered Hæmorrhage was so severe that the operation had to be abandoned A portion of necrotic tumour was removed for examination, and the bleeding was controlled by means of gauze

plugging (Fig 8) A subsequent skiagram revealed erosion of the tenth rib (Fig 8a).

Histological examination of the tumour mass disclosed an alveolar papilliform adenocarcinoma (Figs. 60 and 61). A few days after the operation the liver began to increase rapidly in size. Death occurred thirty-four days after admission to hospital Primary cholangiocellular carcinoma of the liver with metastases in the ribs, lungs and sternum was discovered at autopsy.

Case with Metastases in the Brain.—A Bantu mine labourer aged 30 complained of frontal headache. Shortly after admission to hospital he developed ptosis of the r[illegible] upper eyelid and became semi-conscious. There was fever. His temperature ra[illegible]



FIG. 8 FIG 8a

FIGS 8 and 8a —Showing metastasis in the tenth rib in a case of primary liver cancer The gauze plug controlling hæmorrhage at operation is in position (Fig 8) Note bone absorption in X-ray photograph of the chest wall (Fig. 8a).

between 99° F. and 102° F., and the pulse rate varied between 72 and 90 per minute. Lumbar puncture yielded negative results. "Encephalitis lethargica" was diagnosed. Although his liver was slightly enlarged, the true nature of the condition was not [illegible]

[illegible]

admitted to hospital with a large, smooth, dense spherical swelling in the occipital region of the skull and another in the left anterior chest wall Both tumours appeared to arise from bone and progressed visibly in size The liver was later found to be moderately enlarged Death occurred after twenty-seven days At autopsy the tumours



FIG. 9.—Showing tumours of the occiput and left chest wall due to metastases from a primary liver cancer. The enlarged liver is outlined Note the extreme youth of the patient.

were found to be metastatic growths involving the occiput and the dura mater (Fig. 68) as well as the eighth and ninth ribs, all secondary to primary cancer of the liver.

CASES RECORDED IN THE LITERATURE

Metastases in the Heart.—Weber (1916) recorded a case of unsuspected liver cancer where gross cardiac failure was the only clinical manifestation. The true diagnosis was revealed at autopsy, when primary carcinoma of the liver with metastases in the right auricle and thrombosis of the inferior vena cava were found.

Culpepper and von Haam (1934) reported a similar case. Their patient was an American Negro who exhibited dyspnœa, cyanosis, anasarca and venous distension. A clinical diagnosis of arteriosclerosis was made. Autopsy, however, revealed primary liver cancer with extensive metastases in the right side of the heart and tumour thrombosis of the inferior vena cava

Similar cases were recorded by Jono and Matsuoka (1933) and by Gregory (1939)

Metastases in the Lungs.—The case recorded by McKean (1922) is strikingly similar to the one described by the author His patient complained of expectorating blood-stained sputum, and loss of weight. A provisional diagnosis of tuberculosis was made, but investigation for the tubercle bacillus yielded negative results X-ray examination, however, showed bilateral areas of consolidation suggesting "metastatic" malignancy. The liver became enlarged later Autopsy showed primary liver cancer with metastases in the lungs and kidneys

Metastases in the Brain.—Giachetti (1907) recorded a similar case to that described by the author Here, too, mental changes were predominant There was considerable

asting and the liver was enlarged. Autopsy revealed primary liver cancer with multiple etastatic nodules in the left cerebral hemisphere.

Sudden aphasia and right hemiplegia were the chief symptoms in the case reported y Barre and Paillas (1934)

Metastasis in the Penis.—Gadrat (1930) reported a case with a secondary growth n the corpus cavernosum which produced false priapism.

Metastases to the Skeletal System

Metastasis of primary liver cancer to bone is commonly thought to be rare. Bolker *et al.* (1937), in a review of the literature to 1936, found only 9 such cases. Greene (1939), however, in a ten-year review of 386 cases of hepatoma, found metastases to bone in 8 per cent

Sternum.—The case described by White (1899) was treated for a tumour of the sternum; at no time were there any symptoms pointing to disease of the liver. Death occurred shortly after admission to hospital. Autopsy revealed primary liver cancer with metastases in the sternum, clavicles and tibia

Surbek and Vos (1934) recorded a similar case. Their patient, a Javanese, presented himself for the treatment of a tumour localised to the sternum While in hospital a tumour occupying the hepatic region was discovered, which at autopsy proved to be primary liver cancer with metastases in the sternum.

Clavicle.—Hartmann *et al.* (1936) described a case of secondary hepatoma in the clavicle.

Ribs—Metastases were found in the sixth rib and lungs of a case treated by Mensh and Hanno (1944)

Humerus.—The case recorded by Surbek and Vos (1935) was a Malay who had been admitted to hospital for a neoplasm of the humerus Further examination revealed this to be secondary to primary liver cancer.

The case described by Mouchet *et al* (1922) was a Native labourer who had previously been treated for a fractured humerus, but had returned two months later with spontaneous fracture at the site of the old injury. A tumour was evidently present and the arm was amputated While he was in hospital cancer of the liver was discovered Autopsy revealed that the tumour in the humerus was secondary to the liver cancer

Femur.—Moon (1929) reported the case of spontaneous fracture of the femur in an American Negro who died shortly after admission to hospital. Autopsy revealed latent primary liver cancer with metastasis in the femur at the site of fracture. Similar cases have been described by Catsaris (1921) and by Bolker *et al* (1937).

Spinal Column.—A number of primary liver cancer cases with metastases in the spine have been reported where the sole symptoms pointed to disease of the spine or spinal cord (Blumberg, 1912, Dijkstra, 1925; Brodin *et al.* 1935; Thomson, 1935, Trinca and Willis, 1936, Lynch, 1937, Bronzini, 1947; Mallory, 1947) The symptoms included pain, paraplegia, diplegia and incontinence of urine and fæces. In most cases there was nothing to direct attention to the liver, although immediately before death enlargement of the liver was occasionally noticed The true nature of the condition was discovered only at autopsy.

Skull.—Clairmont (1909) and Prym (1912) have reported cases with skull metastases which had been mistakenly operated upon as primary growths.

Multiple Bone Metastases.—In the case described by Neumann (1944) numerous metastases were present. These involved the skull, cervical and lumbar vertebræ and a rib. A metastasis in the humerus had induced spontaneous fracture.

TABLE XIV

SHOWING PERCENTAGE FREQUENCY OF SYMPTOMS AND SIGNS IN PRIMARY LIVER CANCER (*After Warvi*, 1945)

Symptoms and Signs	*75 Bantu Cases (Author's series)*	*134 Chinese Cases (Tull, 1932)*	*37 Cases at Cincinnati (Warvi, 1945)*	*31 Cases at the Mayo Clinic (Hoyne and Kernohan, 1947)*	*500 Cases reported in the Literature (Warvi, 1945)*
Asthenia	86	89	94	87	88
Abdominal pain	90	9	71	87	52
Dyspnœa	25	—	—	—	—
Loss of weight	83	—	94	71	88
Enlarged liver	100	68	91	58	68
Tender liver	90	15	15	—	17
Jaundice	45	34	80	58	34
Ascites	55	47	37	77	46
Dilated abdominal veins	19	52	—	26	—
Œdema of legs	30	83	40	74	60
Anæmia	100	38	97	42	68
Fever	38	28	52	39	34

CHAPTER IX

DIAGNOSIS

ALL European and American observers are unanimous that primary carcinoma of the liver is a very rare disease—"so rare, perhaps, that one does not entertain the idea until a case arrives" (Dansie, 1922). According to Williamson (1924), "the rarity of primary carcinoma of the liver is such as to make one think a long time before risking such a diagnosis, for the odds are enormously against it" On this account, a correct clinical diagnosis is but seldom made.

Among African and Oriental races, on the other hand, the disease occurs with such great frequency that clinicians readily accept primary liver cancer as a definite clinical entity, and one, moreover, which may be recognised with a certain degree of confidence

Diagnostic Features (Table XIV).—While it is difficult to arrive at a correct clinical diagnosis in a case of liver enlargement without the opportunity of examining the liver directly, the following criteria are suggestive of primary liver cancer. marked preponderance of the disease in males; relatively early age incidence in Africans and Orientals; gradually increasing weakness, emaciation and constant pain in the right upper quadrant of the abdomen; finding a mass in the same situation—obviously the liver—which is tender, nodular, fixed and enlarged (in an upward as well as in a downward direction) often to a remarkable extent; anæmia and increased pulse rate, although the temperature may be normal or subnormal; presence of jaundice, ascites, œdema of the lower extremities and dilatation of the superficial abdominal veins.

These symptoms are especially significant in a suspected case where the gastro-intestinal tract and gall-bladder reveal no evidence of disease on roentgenological examination, and where the liver becomes more tender, increases in size and irregularity and the ascitic fluid becomes hæmorrhagic during the course of observation

[illegible]

favour metastasis, e g the skeletal system

The aforementioned criteria, while favouring the diagnosis, must be considered merely as suggestive evidence of the disease Certain diagnosis is based upon clinical observations, together with the histological findings of material obtained at operation or biopsy

LABORATORY AND OTHER DIAGNOSTIC AIDS

Liver Function Tests.—Most liver function tests devised thus far are of doubtful value, mainly because the liver is an organ with such a great reserve capacity that much of its tissue may be destroyed without producing appreciable signs of deficiency. I have seen many cases where the liver was practically replaced by carcinoma, yet there was a singular absence of jaundice, and all liver function tests proved normal. That the

Liver Aspiration Biopsy.—Liver puncture biopsy is a valuable procedure for establishing the diagnosis in obscure hepatic enlargements where exploratory laparotomy is considered inadvisable.

The method first described by Iversen and Roholm (1939) consists of introducing a long needle-like cannula and stylet through an anæsthetised track into the right lobe of the liver. The stylet is then removed, suction applied with a Record syringe and the apparatus is withdrawn, maintaining suction meanwhile. The aspirated tissue is then prepared for histological examination. Positive cytological findings range from scattered tumour cells to well-defined areas of cancer tissue, characterised by the unmistakable architectural pattern of hepatocellular (Fig. 10) or cholangiocellular cancer.

By this technique Baron (1939) was able to demonstrate metastatic carcinoma in 12 of 18 cases of hepatomegaly, Binkley (1939) diagnosed 19 cases of liver tumour, and Tripoli and Fader (1941) discovered one primary and three secondary liver cancers.

A number of fatalities have been reported as a result of this method, and a large *percentage of aspirations have failed to yield tissue for examination. By modifying the* apparatus and by using the epigastric route to the liver, Gillman and Gillman (1945b) have considerably improved the safety and efficiency of the procedure. In 500 biopsies on 206 Bantu patients they found 11 hepatocellular carcinomas and three secondary cancers of the liver. There was one death from hæmorrhage in a patient with an enlarged liver and spleen which proved to be tuberculous at post-mortem

It is advisable to ascertain the blood prothrombin level before liver biopsy is attempted, and to administer vitamin K in cases with jaundice. A preparatory twelve-hour fast will avoid the possibility of puncturing a distended stomach. After aspiration, firm pressure should be maintained for about five minutes over the puncture site, and the pulse rate watched for any untoward rise for twelve hours.

Duodenal Aspiration.—The Papanicolaou technique (1946), originally used in the examination of vaginal smears, has now been successfully extended by Lemon and Byrnes (1949) to demonstrate exfoliated neoplastic cells in the aspirated duodenal contents of patients with carcinoma of the liver, bile duct or pancreas.

This aspiration method is one, moreover, which has been found of value as a supplementary diagnostic aid in both early and late cancer cases. It is a relatively simple procedure which offers a promising field for clinical research.

CHAPTER X

DIFFERENTIAL DIAGNOSIS OF TYPICAL PRIMARY LIVER CANCER

ALTHOUGH enlargement of the liver is the commonest sign in primary liver cancer, the discovery of a tumour in the right hypochondrium, because of its frequency in other diseases, often gives rise to serious difficulties in diagnosis. In any suspected case the following questions must be answered before a diagnosis can be made:

(1) Is the tumour part of the liver or does it arise from a neighbouring organ?

(2) If the organ involved is the liver, is the enlargement due to local or to general causes?

(3) If malignancy is suspected, does the neoplasm arise primarily in the liver or is it a metastatic growth secondary to cancer in a remote organ?

Diagnosis from Secondary Liver Cancer.—On the question of malignancy it must be remembered that there are a number of organs which, when involved by cancer themselves, are known to be frequent sources of secondary growths in the liver. These organs include the stomach, colon, rectum, gall-bladder, ovary, uterus, mammary gland, kidney, prostate, bladder, mouth, lip, tongue, œsophagus and the eye. It is only after these organs have been definitely excluded by careful examination that the malignancy can be regarded as primary in origin

According to different observers, secondary cancer predominates over primary liver cancer by a large majority, the ratio varying between 65·5 to 1 (Orth, 1909), 40 to 1 (Von Hansemann, 1890) and 25 to 1 (Smith, 1933) This is not the case in Africa and the Orient.

Apart from evidence of a primary growth elsewhere, secondary cancer differs from primary liver cancer by multiplicity of tumours on the surface of the liver; slower increase in size, more intense jaundice; greater frequency of ascites; earlier emaciation; a less rapid course (Rolleston and McNee, 1929)

Diagnosis from Primary Sarcoma of the Liver.—Sarcoma of the liver occurs more rarely than carcinoma. Since the clinical features of the two conditions are practically identical, differentiation between them without biopsy is not possible.

Jaffe (1924) has described a case of primary sarcoma of the liver associated with primary carcinoma of the same organ, and referred to two other such cases in the literature

Diagnosis from Benign Liver Tumours.—This is often extremely difficult, since many primary liver cancers remain symptomless until the final stages of the disease; or are characteristically latent, being discovered only by accident or at post-mortem (*see* Occult Cancer)

Many of the early symptoms are similar in both types of tumour, including fullness of the epigastrium, vague indigestion and vomiting Fluctuation in an otherwise symptomless enlarged liver is suggestive of cystic adenoma A mass which has existed

for many months or years and is slowly growing is indicative of a simple rather than a malignant tumour.

Again, in benign tumours there is not the distinct pain so frequently associated with carcinoma, nor is there weakness, elevation in temperature and pulse rate, loss of weight, anæmia, ascites, fixation of the diaphragm or peripheral œdema. Where the hilum is compressed, jaundice may occur in either condition. It must be remembered that adenomata may result in cancerous transformation, as was exemplified by Willis (1943) in a case of carcinoma arising in a developmental cyst.

DIAGNOSIS FROM CERTAIN OTHER DISEASES PRODUCING LIVER ENLARGEMENTS

Venous Congestion of the Liver.—Congestive cardiac failure may present features simulating primary carcinoma of the liver. There may be hæmatemesis, ascites, anascara and slight jaundice. In chronic venous engorgement, the liver is uniformly enlarged, tender on pressure, and may sometimes be seen to pulsate. Detection of the cause—e.g. valvular disease of the heart, myocardial insufficiency, fibrosis of the lungs, emphysema, chronic nephritis and essential hypertension, or the effect of treatment in diminishing signs and symptoms—will reveal the true nature of the disease.

Abdominal Tuberculosis.—This condition often causes difficulty in diagnosis in the Bantu, who are highly susceptible to this form of tuberculosis In abdominal tuberculosis there may also be ascites, hepatic enlargement and muscular wasting. The ascitic fluid is of a higher specific gravity and is richer in albumen than in cancer of the liver: it may contain lymphocytes. Matting of the intestines may occasionally be felt. The temperature is usually more elevated than in primary carcinoma of the liver.

***Portal Cirrhosis.**—The liver may be enlarged, but this enlargement is usually* uniform. There may be ascites which requires aspiration before the liver can be palpated. The nodules are small, are uniform in size and not as variable as in cancer. Emaciation and pain are not as pronounced as in primary carcinoma of the liver. Jaundice is transient and often intermittent. There may be a history of alcoholism, dyspepsia and hæmatemesis. Progressive increase in size is in favour of a tumour, particularly if it affects one lobe only. Where carcinoma supervenes upon existing cirrhosis, the diagnosis may be difficult

Syphilis of the Liver.—In gumma the onset is more insidious and the liver does not usually attain the great size reached by a cancerous liver, nor is the course of the enlargement so rapid. It is harder, is not so painful and is less irregular. The nodules are frequently single, firmer and smaller than in cancer. Jaundice and ascites are usually transient A history of syphilis, a positive Wassermann reaction and effective anti-syphilitic treatment help to settle the diagnosis

Cholelithiasis.—In the presence of gall-stones the liver may assume a uniform enlargement Jaundice, though present, may be intermittent. The pain is of sudden onset, agonising in character and intermittent. Cholecystography will assist in indicating the true nature of the disease Among the Bantu, cholelithiasis is rare.

Chronic Malaria.—Enlargement of the liver with tenderness to palpation sometimes results from chronic malaria, and is accompanied by splenic enlargement and intermittent fever The patient may be emaciated The history, blood smear examinations,

the presence of tertian or quartan periodicity and the beneficial response to treatment will indicate the true nature of the disease.

Amyloid Disease.—A large amyloid liver in an emaciated patient may be mistaken for primary liver cancer, but the preservation of its shape, the evidence of chronic disease elsewhere, the absence of pain and of rapidly progressive enlargement of the liver with a history of past suppuration will help in the diagnosis.

Leukæmia—The liver may be enlarged, but is smooth and regular in shape. Epistaxis and hæmatemesis often occur and the spleen is greatly enlarged. A blood examination will settle the diagnosis.

Banti's Disease.—Here there is splenic enlargement, but the liver is not as large nor is the cachexia as pronounced as in cancer. Hypochromic anæmia, often associated with leucopenia, and hæmatemesis or melæna may be present.

Cystic Disease of the Liver.—The liver is enlarged Cystic changes may be present in the kidneys as well, rendering them palpable. The symptoms are then renal rather than hepatic.

Ptosis of the Liver.—Other abdominal organs may be displaced also. The severe constitutional symptoms found in cancer are absent. By percussion it is possible to demonstrate that the upper border of the liver is abnormally low.

Diagnosis from Tumours of Neighbouring Organs

Carcinoma of the Pylorus.—A tumour may be felt in the upper right quadrant of the abdomen It is often movable, but when very large and fixed, differentiation from the liver may be difficult There may be digestive disturbances, nausea and hæmatemesis. Radiological investigation will assist in determining the diagnosis.

Carcinoma of the Transverse Colon.—The tumour is hard, rarely painful and often movable There may be abdominal discomfort and constipation alternating with diarrhœa Blood and mucus may be seen in the stools, and in cases approaching intestinal obstruction there may be visible peristalsis. Radiological examination following a barium enema will help to clarify the diagnosis.

Tumours of the Right Kidney.—Tumours of the right kidney may appear to be continuous with the liver, but a vertical band of colonic resonance over an otherwise dull mass may be detected in front of the tumour. Hæmaturia, pyuria and albuminuria would be evidence of renal disease. There is no jaundice, unless the bile duct is compressed

Tumours of the Right Adrenal Gland.—Large growths may cause difficulty in diagnosis As in primary liver cancer, metastases may be formed in the liver, lungs, skull and vertebræ There may be general adiposity, sexual precocity and suggestions of Addison's disease.

Tumours of the Head of the Pancreas.—These may produce distension of the gall-bladder and jaundice of gradually increasing intensity by compressing the common bile duct or by invading its orifice. The mass felt may be difficult to distinguish from an enlarged liver Glycosuria and fatty stools would be evidence in favour of a pancreatic tumour

CHAPTER XI

DIFFERENTIAL DIAGNOSIS OF ATYPICAL PRIMARY LIVER CANCER

ACUTE ABDOMINAL CANCER

HÆMORRHAGE from sudden rupture of a cancerous nodule in the liver is a catastrophe which offers great difficulty in distinguishing primary carcinoma of the liver from the following acute abdominal emergencies:

Perforated Gastric or Duodenal Ulcer.—There is a previous history of abdominal pain related to food. The patient suddenly develops agonising pain in the epigastric region, accompanied by tenderness and boardlike rigidity of the abdominal muscles The pulse at first is slow, becoming rapid later. Vomiting is usually late and the liver dullness may be diminished or absent.

Perforation of the Small Intestine.—Signs of an abdominal catastrophe may be the first indication of the disease in ambulatory typhoid.

Volvulus of the Small Intestine.—This is a rare condition in Western countries, but is fairly frequent among the Bantu There is a sudden onset of severe, diffuse, abdominal pain accompanied by vomiting, constipation and abdominal distension.

Rupture of the Liver or Spleen.—A history of severe violence, such as a crush injury or blow in the abdomen, is obtained Where the spleen is enlarged following chronic malaria, as in tropical inhabitants, even slight trauma is known to produce severe internal hæmorrhage

Acute Appendicitis.—The onset of pain at the umbilicus, later shifting to the right iliac fossa, persistent vomiting, rise in temperature, leucocytosis and signs pointing to a lesion in the right iliac fossa favour acute appendicitis. Appendicitis is rare in the Bantu

Acute Pancreatitis.—The attack begins suddenly with severe agonising abdominal pain which is unrelieved even by morphia. There is prostration and collapse, a tendency to cyanosis and air hunger, marked epigastric tenderness, distension and persistent vomiting. On abdominal section fat necrosis may be encountered.

Biliary Colic.—The onset of pain in the right hypochondrium is agonising and sudden. It is accompanied by collapse, vomiting, and profuse perspiration. The termination of the attack is equally sudden Gall-stones and cholecystitis are rare in the Bantu

Renal Colic.—The pain is most marked over the kidney region, is severe, and may radiate along the line of the ureter to the external abdominal ring or the testis In a severe attack vomiting may occur and the abdomen may become rigid. The thigh may be flexed on the affected side, there may be a desire to micturate frequently, and hæmaturia. Radiological examination of the kidney and ureter may reveal a calculus

Mesenteric Thrombosis.—Although rare, mesenteric thrombosis may occur in patients suffering from infective endocarditis, mitral stenosis, general arterial degeneration, or

cirrhosis of the liver. The onset is sudden, with general symptoms of acute intestinal obstruction. There is hæmatemesis and diarrhœa, accompanied by considerable quantities of blood.

Febrile Cancer

In rapidly growing tumours the general constitutional symptoms, including pyrexia and tachycardia associated with enlarged tender livers, always offer great difficulties in distinguishing primary liver cancers from the more common hepatic suppurations.

Amœbic Abscess of the Liver.—This is relatively common in tropical and sub-tropical regions such as South Africa. Fever is usually more marked than in primary carcinoma of the liver and is often of an intermittent or septic variety. Rigors may occur. The liver is enlarged and tender. Infrequently, œdema of the abdominal wall over the liver may be detected. There may be a previous history of dysentery and the *Entamœba histolytica* may be found in the stools. Leucocytosis is present. Aspiration of the liver may yield chocolate-coloured pus.

[illegible]

[illegible]

not marked. It occurs usually in early adult life. The liver tumour is rounded, smooth and regular, and is neither tender nor painful. A "hydatid thrill" may sometimes be felt. Hooklets may be found in the fluid aspirated from the liver. There is no jaundice and ascites is rare Cachexia occurs only after the disease has persisted for some time. A positive hydatid complement fixation test is of diagnostic value. The blood picture is often characterised by eosinophilia

Subphrenic Abscess.—In a large subphrenic abscess the displaced liver may become palpable. This, together with constitutional disturbances, may simulate a rapidly growing primary liver cancer. There may be a previous history of gastric or duodenal ulcer or appendicitis The onset is acute, with pain in the upper abdomen and the right shoulder, fever, rigors and cough Leucocytosis is present. Exploratory puncture through one of the lower intercostal spaces may yield pus Radiological examination will help in the diagnosis

CHAPTER XII

PROGNOSIS AND TREATMENT SUMMARY OF CLINICAL MANIFESTATIONS

PROGNOSIS

THE outlook of primary carcinoma of the liver is hopeless, for it is *generally rapidly fatal*. In my own series of 75 cases, *duration of the disease was never more than four months* from the first appearance of symptoms, and the stay in hospital varied from one to eighty-one days, the average being twenty days.

The most rapidly fatal cases were observed in Groups II ("acute abdominal" cancer) and III ("febrile" cancer). Four of the 6 cases in Group II died from intraperitoneal hæmorrhage on the day of admission to hospital; the remaining 2 survived abdominal section by twenty-seven and thirty-one days respectively. *The extremely malignant* nature of the growth associated with Group III was demonstrated by the fact that the average stay in hospital was only nine days

Indications of approaching death are *sudden marked enlargement of the liver*, rapidly intensifying jaundice, increased dilatation of the superficial abdominal veins and additional œdema of the extremities.

TREATMENT

Medical.—Owing to the hopelessness of the disease, treatment is essentially palliative, and is directed towards the relief of pain and discomfort. Sedatives are always required in large and increasingly frequent doses.

Radiotherapy.—It is possible that radiotherapy may prove of value in treating early stages of the disease. By the time the patient presents himself, however, *the disease is* so far advanced that it is apparently beyond cure I have been unable to study the effects of radiotherapy owing to lack of facilities. There is a singular dearth of references concerning the effects of radiotherapy on primary liver cancer. I have found only two reports in the literature: radium therapy was used by Abbe (1911), roentgen therapy by Warvi (1944)—both without success.

Radioactive Substances.—The use of isotopes in the treatment of primary liver cancer has been suggested by the action of labelled anhydrous chromic phosphate, an insoluble radioactive compound. Jones *et al.* (1944) showed that *when an aqueous suspension of this compound is given intravenously* to laboratory animals, it is taken up largely by the reticulo-endothelial system of the liver, spleen and bone marrow.

This compound has been used therapeutically by intravenous injection without toxic effects Low-Beer *et al* (1942) found a definite though temporary benefit in a case of melanosarcoma with extensive liver metastases The selective action of chromic phosphate suggests that radioactive substances may be of value in treatment, and should be tried in the rapidly growing tumours seen so frequently in Africa and the Orient.

Surgery.—The question of surgical treatment must be considered, especially if during the course of an operation undertaken for some other condition a single suspicious nodule is encountered in the liver. Experience has shown, however, that surgical treatment is unsatisfactory, for the resection of a malignant growth from the liver is no guarantee of a permanent cure.

The decision to resect such a tumour by partial lobectomy depends upon whether it is solitary, is not unduly large, has clearly defined margins, and, especially, if it affects the left lobe. In such a case the excision should be wide and should embrace a liberal portion of the outlying healthy tissue. Due care must be taken to control hæmorrhage, as bleeding may assume alarming proportions.

In the author's series of cases all attempts at radical cure had to be abandoned, as [illegible]

only twice

Thus far 31 cases have been recorded in the available literature where attempts at surgical removal of the tumour were made Of these, 8 cases died within sixteen days [illegible]

7 months.

Partial lobectomy has proved most successful in cancers involving the left lobe of the liver Brunschwig (1947), however, has instanced a case of a large carcinoma involving most of the right lobe which, together with the adherent gall-bladder, was successfully resected. Two years later the patient was again operated upon for recurrence in the retroperitoneal glands These, together with the right colon, were removed, and the patient survived seven years He died nine years after the original operation from carcinomatosis, including involvement of the markedly hypertrophied left lobe of the liver

Summary of Clinical Manifestations

1 Primary liver cancer is pre-eminently a disease of males. Among the Bantu and Javanese, young adults below the age of 40 are chiefly affected. Among other races, it is commonest after middle age Children of all ages are not infrequently affected.

2 Heredity, trauma and cholelithiasis do not appear to be important ætiological factors.

3 On symptomatological grounds cases of primary liver cancer are classified into five clinical Groups I, "frank" cancer (62 7 per cent. of cases); II, "acute abdominal" cancer (8 per cent), III, "febrile" cancer (8 per cent); IV, "occult" cancer (16 per

cent.); and V, "metastatic" cancer (5 3 per cent. of cases). Of these Group I, is typical, Groups II–V, are atypical.

4. In "frank" cancer the signs and symptoms are referred to the liver from the beginning in patients previously in good health. The mode of onset is gradual. The symptoms include: asthenia, 86 per cent. of cases; abdominal pain, 90 per cent. of cases; dyspnœa, 25 per cent. of cases.

The physical signs are: loss of weight and emaciation, 83 per cent. of cases; enlargement of the liver, 100 per cent.; tenderness of the liver, 90 per cent.; jaundice, 45–60 per cent.; ascites, 55–72 per cent.; dilatation of the superficial abdominal veins, 19–52 per cent ; peripheral œdema, 30–83 per cent. of cases. Fatal hæmatemesis may occur. Secondary anæmia is frequent. There may be a venous hum over the liver. Varying degrees of gynæcomastia and testicular atrophy have been reported. The pulse rate and temperature may be elevated, and the spleen may be enlarged.

5. In "acute abdominal cancer" the patients, previously unaware of the disease, suddenly develop acute surgical catastrophes of the abdomen due to rupture of carcinomatous nodules or erosion of blood-vessels on the free surface of the liver. The immediate mortality rate is high. Those cases which survive operation may later develop the clinical picture of "typical" liver cancer.

6. In the "febrile" group, the most rapidly growing form of primary liver cancer, symptoms are not unlike those of amœbic liver abscess.

7. Cases of "occult" cancer are usually discovered either during routine examination for complaints other than those attributable to disease of the liver, or accidentally at autopsy.

8. In "metastatic" cancer symptoms due to secondary growths in remote organs completely overshadow the primary liver lesion. Any structure can be involved in this way, including the heart, lungs, brain and skeletal structures.

9. Primary liver cancer may simulate a large number of diseases.

10. The diagnosis is established on clinical grounds, together with the histological findings of material obtained at operation or biopsy.

11. All liver function tests devised thus far are of doubtful value in primary liver cancer.

12. Among the laboratory and other procedures which have proved helpful as diagnostic aids are the following the icteric index; Takata-Ara reaction; alkaline phosphatase test; lactic acid content of blood; roentgenological findings; peritoneoscopy; liver aspiration biopsy, duodenal aspiration for cancer cells

13. The prognosis is hopeless. The disease rarely lasts longer than four months from the first appearance of symptoms; the usual stay in hospital is three weeks. The most rapidly fatal cases occur among the "acute abdominal" and "febrile" types of cancer.

14. Treatment is essentially palliative Surgical intervention is usually impracticable, except in the rare cases involving the left lobe of the liver.

PART III

MORBID ANATOMY

CHAPTER XIII

GROSS PATHOLOGY

Weight of the Liver.—The liver is always increased in weight—often to a remarkable degree In my series of cases, accurate weights of cancerised livers were recorded in 51 instances, an analysis of which is given in Table XV.

TABLE XV

Grm	*No of Cases*
1,900–2,500	8
2,501–3,500	17
3,501–4,500	8
4,501–5,500	13
5,501–6,500	2
6,501–7,100	3
Total	51

The maximum weight observed in any individual case was 7,100 grm.; the minimum, 1,900 grm ; the average, 3,870 grm. (The average weight of a normal adult male Bantu liver is 1,750 grm.)

Situation of Tumours in the Liver.—The right lobe is the common site of involvement. In my series of 63 cases, where accurate records were available, the disease attacked the right lobe alone in 24 cases, and the left lobe in 1 case. In 38 cases both lobes were involved, but here the right lobe invariably bore the brunt of the disease.

According to McIndoe and Counsellor (1927), the liver is, in a sense, a symmetrical organ, with the right and left lobes possessing

the portal vein Venous blood from the duodenum, head of the pancreas and jejunum passes to the right lobe of the liver, whereas venous blood from the stomach and spleen passes to the left lobe.

It is highly probable that carcinogenic agents (including chemical compounds, products of metabolism and internal secretions) may in this way be absorbed from the small intestine, "streamlined" via the portal vein directly into the right lobe of the liver, and there initiate those processes which will lead to carcinoma. The tumour thus formed may remain localised entirely to the right lobe of the liver, or it may subsequently invade the left lobe by direct infiltration or by intrahepatic hæmatogenous

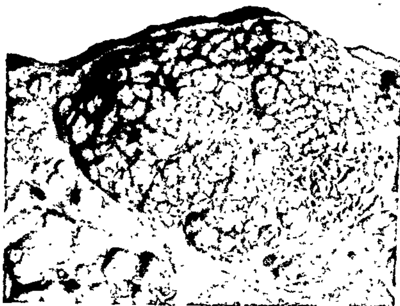


FIG. 11.—External appearance of portion of "nodular" liver cancer, showing aggregation of tumour masses



FIG 12.—Section through "nodular" liver cancer, showing tumour masses of varying shapes and sizes, discrete as well as confluent, occupying the right lobe of the liver. Note that the left lobe is unaffected, but is the seat of cirrhosis



FIG 13—Section through "nodular" liver cancer, showing the whole liver studded with round discrete carcinomatous nodules which practically replace all normal tissue.

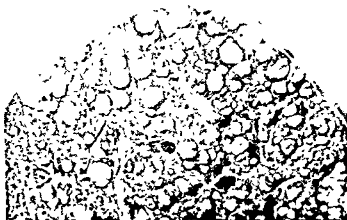


FIG 14—Section through portion of "nodular" liver cancer, showing character of nodules Note dark-coloured hæmorrhagic nodules

spread. It is probably on this account that tumours in the left lobe of the liver, being more recent, are invariably smaller than those in the right lobe.

Classification.—For practical and descriptive purposes, primary liver cancer can be divided macroscopically into two groups, namely, "nodular carcinoma," i e. a tumour formed of numerous discrete nodules or bosses, and "massive carcinoma," i.e. a tumour consisting mainly of a single large dense mass.

It must be understood, however, that a sharp demarcation between these two groups is scarcely possible, for many tumours originally nodular in character often show tendencies towards transformation into massive cancers, and *vice versâ*. By taking the most prominent features of the tumour into account, I was able to divide my own series of cases into 57 per cent. "nodular" and 43 per cent. "massive" cancers.



FIG 15.—Section through "nodular" form of primary liver cancer, showing mosaic pattern formed by close grouping of the nodules

I am of the opinion that "infiltrative" and "cirrhotic" liver cancers, two additional groups met with in the literature, are superfluous, since infiltration is not a distinctive trait, but is common to all cancers, whilst cirrhosis is intimately associated with the majority of primary liver cancers.

NODULAR CARCINOMA

External Appearance.—In this group the liver is large, hard, scarred, deformed and studded with closely grouped or widely separated irregular nodular masses (Fig. 11) which vary from a few millimetres to several centimetres in diameter. They are whitish, greyish-yellow or dark green in colour, are covered by a thickened Glisson's[4] capsule, and though usually firm in consistency, may be fluctuant on palpation Umbilication is not present.

The normal tissue intervening between these nodules is brownish in colour and shows evidence of passive congestion. Adhesions may be present between the nodules and such neighbouring organs as the omentum, stomach, transverse colon, duodenum, gall-bladder and particularly the diaphragm.

Where the immediate cause of death has been due to intraperitoneal hæmorrhage (as happens in "acute abdominal" cancer), or in cases with hæmorrhagic ascites, bleeding can always be traced to a necrotic nodule which has ruptured through the liver capsule

Internal Appearance.—Increased resistance to the knife in the liver tissue is always encountered on section The liver substance is replaced in part (Fig. 12) or throughout (Fig. 13) by multiple nodular tumour masses which are either rounded or oval in shape (Fig 14) In most cases the nodules differ markedly in size, varying in the same specimen from a few millimetres to over 10 cm in diameter. Usually they are



FIG 16—Section through portion of "nodular" carcinoma of the liver, showing lobulated appearance of the tumour masses (Enlarged portion of Fig 12)



FIG 17—Section of "nodular" carcinoma of the liver, showing aggregation of nodules towards the periphery of the liver



FIG 18 —Section through "nodular" form of primary liver cancer, showing irregular size and shape of cancer nodules, confluence of nodular masses and at (*a*) a large tumour thrombus in the portal vein



FIG 19 —Section of "nodular" carcinoma of the liver, showing variation in size and shape of the nodules and tendency towards confluence

scattered throughout the liver parenchyma in a haphazard manner, but they are often closely grouped together (Fig 14), assume a mosaic pattern (Fig. 15), or present a peculiar lobulated appearance (Fig. 16) The nodules are most prevalent at the periphery of the liver (Fig. 17), where they account for the distorted appearance of its surface.

Depending upon the secondary changes within the tumour, the colour of the cut surface is either yellow, grey, white, green, brown or red; yellow and grey, however, predominate. The nodules are usually of firm consistency, but friable nodules are frequently encountered By light pressure the latter may be enucleated readily, when they are observed to lie within the portal and hepatic veins as cancerous thrombi (Fig. 18). These tumour thrombi are of especial significance, for they are the chief means of intrahepatic and extrahepatic metastatic spread. With extensive liquefaction, necrosis or hæmorrhage, the tumour may assume a cystic appearance.

Grey translucent bands of fibrous tissue separate the nodules from one another and are often seen to penetrate into the liver parenchyma, where they join marked cirrhotic tracts. The intervening liver tissue is greatly compressed or atrophied and may lose its normal pattern. Obvious infiltration of the tumour masses is a usual feature, but nodules are occasionally found surrounded by thick fibrous tissue. Frequently, tumour nodules in the same specimen tend to become confluent, thus forming transitions to the "massive" type of cancer (Figs. 18 and 19). Here the distinguishing feature between "nodular" cancer and the frankly "massive" type is that at the periphery of the coalescing mass a number of more or less discrete nodules can be discerned

Thus, in Fig 19 the appearance in the left lobe is suggestive of "massive" carcinoma, but a close examination reveals that the tumour mass consists of multiple confluent nodules remaining particularly discrete at the periphery. These appearances may be looked upon as transitions between "nodular" and "massive" cancer.

MASSIVE CARCINOMA

External Appearance.—As in "nodular" cancer, the "massive" type produces enormous enlargement of the liver, and was responsible for the heaviest and largest livers in my series. The liver of one of my cases weighed 7,100 grm, and is one of the largest livers on record (Fig 20)

At the site involved, usually the right lobe, there is a uniform smooth swelling, often with a few small dilated blood-vessels coursing along its periphery. Such a tumour mass often reaches the dimensions of a full-term fœtal head.

Occasionally there is secondary irregularities which produce bosses beneath the *capsular surface Both the major and minor swellings often* cause gross distortion of the entire organ (Fig 20) Over the tumour masses Glisson's capsule is greatly thickened, and firm adhesions between it and the diaphragm and adjacent organs are often encountered.

Internal Appearance.—On section, the tumour may be found virtually confined to one lobe (Fig. 21), but more frequently there is a massive growth occupying practically the whole of one lobe (usually the right) with multiple smaller growths in the other (Fig 22) These latter are particularly localised to the periphery (Fig. 23).